Registries for Evaluating Patient Outcomes: A User's Guide

Third Edition

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Registries for Evaluating Patient Outcomes: A User's Guide

Third Edition

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Preface

This project was performed under a contract from the Agency for Healthcare Research and Quality (AHRQ) in collaboration with the Centers for Medicare & Medicaid Services (CMS) through the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network of AHRQ's Effective Health Care (EHC) Program. The purpose of the project was to update and expand *Registries for Evaluating Patient Outcomes: A User's Guide*. The User's Guide was first published in 2007 as a reference for establishing, maintaining, and evaluating the success of registries created to collect data about patient outcomes. The second edition, which provided updates to the existing topics and addressed four new topics, was published in 2010. The purpose of this revised and expanded third edition is to incorporate information on new methodological and technological advances into the existing chapters and to add new 11 chapters to address emerging topics in registry science.

Both the 2007 and 2010 versions and this third edition were created with support from a large group of stakeholders. Following award of the initial project on September 29, 2005, we created a draft outline for the document, which was posted for public comment on AHRQ's Effective Health Care Web site (www.effectivehealthcare.ahrq.gov) from January through March 2006. During that same period, we worked with AHRQ to create a process for selecting contributors and reviewers. We broadly solicited recommendations from a range of stakeholders, including government agencies, industry groups, medical professional societies, and other experts in the field; conducted a review of the pertinent literature; and contacted the initial list of contributors to confirm their interest and area of expertise and to seek further recommendations. Through that process and in collaboration with AHRQ and CMS, we arrived at a set of contributors and reviewers based on subject/content expertise, practical experience, and interest and availability, with balanced representation from key stakeholder groups for nearly all chapters. In addition, a request for submission of real-world case examples that could be used in the user's guide to illustrate issues and challenges in implementing registries was posted on the Effective Health Care Web site. The primary selection criteria for these examples concerned their utility in illustrating a practical challenge and its resolution.

An initial meeting of contributors was convened in February 2006. A second meeting including contributors and chapter reviewers was held in June 2006, following creation of an initial draft document and focused review by the reviewers. The collaborative efforts of contributors, reviewers, and editors resulted in a draft document that was posted for public comment on the Effective Health Care Web site in October and November 2006. In all, 39 contributors and 35 individual reviewers participated in the creation of the first document, which was released in April 2007 and has been published online and in print.

In August 2008, the user's guide update project was awarded. The project involved revising the existing chapters and case examples, creating new content to address four topics, and soliciting new case examples. From September to November 2008, we worked with AHRQ to select contributors and content reviewers for the new user's guide. We followed a process similar to that used in the creation of the original user's guide to arrive at a set of contributors and reviewers with subject matter expertise and a broad range of perspectives. The contributors drafted white papers on four topics: use of registries in product safety assessment, when to stop a registry, interfacing registries and electronic health records, and linking registry data. The white papers were reviewed and discussed at a meeting in April 2009. The papers were then posted for public comment in August and September 2009. After the papers were revised in response to public comments, the final papers were included in the expanded user's guide.

During the same timeframe, we contacted the authors and reviewers of the 2007 version of the user's guide. We asked authors and reviewers to update the existing chapters to address any new

methodological, technological, or legal topics. The revised chapters were circulated for review and discussed at a meeting in July 2009. We also posted a new call for case examples on the Effective Health Care Web site in June 2009. The primary selection criteria for the new examples concerned their utility in illustrating issues and challenges related to the new topics addressed in the white papers. In addition, we contacted authors of the original case examples to obtain updated information on the registries.

In September 2010, the project to create the third edition of the user's guide was awarded. The project involved revising the existing chapters and case examples, creating new content to address 11 topics, and soliciting new case examples. From October to December 2010, we followed a process similar to that used in the creation of the second edition to select contributors and reviewers with subject matter expertise and a broad range of perspectives. Beginning in January 2011, contributors drafted white papers on 11 new topics: registry transitions, analyzing linked data sets, patient identity management, informed consent for registries, protection of registry data, public-private partnerships, using patient-reported outcome measures in registries, rare disease registries, pregnancy registries, quality improvement registries, and medical device registries. The white papers were reviewed and discussed at a series of meetings beginning in July 2011 and ending in October 2011. The papers were then posted for public comment in the spring and summer of 2012. After the papers were revised in response to public comments, the final papers were included in the expanded user's guide.

During the same timeframe, we contacted the authors and reviewers of the 2010 version of the user's guide. We asked authors and reviewers to update the existing chapters to address any new methodological, technological, or legal topics. The revised chapters were circulated for review and discussed at a meeting in July 2012. We also posted a new call for case examples on the Effective Health Care Web site in the spring of 2012. The primary selection criteria for the new examples concerned their utility in illustrating issues and challenges related to the new topics addressed in the white papers. In addition, we contacted authors of the original case examples to obtain updated information on the registries.

For both the 2007 and 2010 versions and this third edition, the contributors and reviewers participated as individuals and not necessarily as representatives of their organizations. We are grateful to all those who contributed to both documents, and who reviewed them and shared their comments.

To begin the discussion of registries, we would like to clarify some distinctions between registries and clinical trials. Although this subject is further discussed in Chapter 1, we offer here the following distinctions from a high-level perspective. The clinical trial is an experiment in which an active intervention intended to change a human subject's outcome is implemented, generally through a randomization procedure that takes decisionmaking away from the practitioner. The research protocol describes inclusion and exclusion criteria that are used to select the patients who will participate as human subjects, focusing the experiment on a homogeneous group. Human subjects and clinical researchers agree to adhere to a strict schedule of visits and to conduct protocol-specific tests and measurements.

In contrast, registries use an observational study design that does not specify treatments or require any therapies intended to change patient outcomes (except as specific treatments or therapies may be inclusion criteria). There are generally few inclusion and exclusion criteria in an effort to study a broad range of patients to make the results more generalizable. Patients are typically observed as they present for care, and the data collected generally reflect whatever tests and measurements a provider customarily uses.

Patient registries represent a useful tool for a number of purposes. Their ideal use and their role in evidence development, design, operations, and evaluation resemble but differ from clinical trials in a number of substantive ways, and therefore they should not be evaluated with the same constructs. This user's guide presents what the contributors and reviewers consider good registry practices. Many

registries today may not meet even the basic practices described. On the whole, registry science is in an active state of development. This third edition of the user's guide is an important step in developing the field.

This book is divided into six sections: Creating a Registry; Legal and Ethical Considerations for Registries; Operating Registries; Technical, Legal, and Analytic Considerations for Combining Registry Data with Other Data Sources; Special Applications in Registries; and Evaluating Registries. The first three sections provide basic information on key areas of registry development and operations, highlighting the spectrum of practices in each of these areas and their potential strengths and weaknesses. Section I, "Creating Registries," includes six chapters. "Patient Registries" defines and characterizes types of registries, their purposes, and uses, and describes their place within the scope of this document. "Planning a Registry" focuses on the recommended steps in planning a registry, from determining if a registry is the right option to describing goals and objectives. "Registry Design" examines the specifics of designing a registry once the goals and objectives are known. "Data Elements for Registries" provides a scientific and practical approach to selecting data elements. "Use of Patient Reported Outcomes in Registries" discusses the role that patient-reported outcome measures play in registries and addresses factors in selecting and using these types of measures. "Data Sources for Registries" addresses how existing data sources (administrative, pharmacy, other registries, etc.) may be used to enhance the value of patient registries.

Section II, "Legal and Ethical Considerations for Registries" highlights the major legal and ethical issues that should be considered when developing and operating a registry. "Principles of Registry Ethics, Data Ownership, and Privacy" reviews several key legal and ethical issues that should be considered in creating or operating a registry. "Informed Consent for Patient Registries" discusses how informed consent for patient registries differs from that of clinical trials and offers suggestions for creating informed consent documents that address the unique aspects of registries. "Protection of Registry Data from Litigation and Other Confidentiality Concerns for Providers, Manufacturers, and Health Plans" reviews the legal protections available for data about providers, manufacturers, and health plans contained in registries.

Section III, "Operating Registries," provides a practical guide to the day-to-day operational issues and decisions for producing and interpreting high-quality registries. "Recruiting and Retaining Participants in the Registry" describes strategies for recruiting and retaining providers and patients. "Data Collection and Quality Assurance" reviews key areas of data collection, cleaning, storing, and quality assurance for registries. "Adverse Event Detection, Processing, and Reporting" examines relevant practical and regulatory issues. "Analysis, Interpretation, and Reporting of Registry Data to Evaluate Outcomes" addresses key considerations in analyzing and interpreting registry data. "Modifying and Stopping Registries" discusses the process of modifying an existing registry as well as considerations for determining when to end a registry.

Section IV, "Technical, Legal, and Analytic Considerations for Combining Registry Data with Other Data Sources," reviews several issues related to the emerging trend of linking or integrating registry data with other data sources, such as electronic health records, administrative databases, or other registries. "Interfacing Registries With Electronic Health Records" describes the current state of electronic health record (EHR) integration technology and maps out potential options for developing interfaces between registries and EHRs. "Linking Registry Data with Other Data Sources to Support New Studies" discusses the technical and legal issues surrounding the linkage of registry data with other data sources. "Managing Patient Identity across Data Sources" reviews the options and strategies for linking patient information stored in multiple databases without the use of full personal identifiers. "Analysis of Linked Registry Datasets" addresses issues that must be considered when analyzing combined or linked registry data, as well as issues related to using registry data to support secondary research studies.

Section V, "Special Applications in Patient Registries," highlights several specific types of patient registries that face unique challenges. "Use of Registries in Product Safety Assessment" describes the utility and challenges of designing a registry to assess safety. "Rare Disease Registries" discusses the increasing interest in using registries to study rare disease, as well as the challenges in design, recruitment, retention, and analysis. "Pregnancy Registries" reviews the value of registries for understanding the effects of medication used during pregnancy and the challenges related to design, recruitment, analysis, and dissemination of results. "Quality Improvement Registries" examines the ability of registries to support efforts to improve quality of care through the use of specialized tools and reports. "Registries for Medical Devices" addresses the unique aspects of medical devices that must be considered in the development and analysis of a registry. "Public-Private Partnerships" provides a review of public-private partnership models for supporting registries as well as a discussion of major considerations for planning and operating a registry using this type of model.

Interspersed throughout the first five sections of the user's guide are case examples. As discussed above, the choice of examples was limited to those submitted for consideration during the 2007, 2009, and 2012 public submission periods. The purpose of their inclusion is solely to illustrate specific points in the text from real-world examples, regardless of whether the source of the example is within the scope of the user's guide as described in Chapter 1. Inclusion of a case example is not intended as an endorsement of the quality of the particular registry, nor do the case examples necessarily present registries that meet all the criteria described in Chapter 25 as basic elements of good practice. Rather, case examples are introduced to provide the reader with a richer description of the issue or question being addressed in the text. In some cases, we have no independent information on the registry other than what has been provided by the contributor.

Section VI is "Evaluating Registries." This final chapter on "Assessing Quality" summarizes key points from the earlier chapters in a manner that can be used to review the structure, data, or interpretations of patient registries. It describes good registry practice in terms of "basic elements" and "potential enhancements." This information might be used by a person developing a registry, or by a reviewer or user of registry data or interpretations derived from registries.

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Senior Editors

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Executive Summary

Defining Patient Registries

This user's guide is intended to support the design, implementation, analysis, interpretation, and quality evaluation of registries created to increase understanding of patient outcomes. For the purposes of this guide, a patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. A registry database is a file (or files) derived from the registry. Although registries can serve many purposes, this guide focuses on registries created for one or more of the following purposes: to describe the natural history of disease, to determine clinical effectiveness or cost-effectiveness of health care products and services, to measure or monitor safety and harm, and/or to measure quality of care.

Registries are classified according to how their populations are defined. For example, product registries include patients who have been exposed to biopharmaceutical products or medical devices. Health services registries consist of patients who have had a common procedure, clinical encounter, or hospitalization. Disease or condition registries are defined by patients having the same diagnosis, such as cystic fibrosis or heart failure.

Planning a Registry

There are several key steps in planning a patient registry, including articulating its purpose, determining whether it is an appropriate means of addressing the research question, identifying stakeholders, defining the scope and target population, assessing feasibility, and securing funding. The registry team and advisors should be selected based on their expertise and experience.

The plan for registry governance and oversight should clearly address such issues as overall direction and operations, scientific content, ethics, safety, data access, publications, and change management. It is also helpful to plan for the entire lifespan of a registry, including how and when the registry will end and any plans for transition at that time.

Registry Design

A patient registry should be designed with respect to its major purpose, with the understanding that different levels of rigor may be required for registries designed to address focused analytical questions to support decisionmaking, in contrast to those intended primarily for descriptive purposes. The key points to consider in designing a registry include formulating a research question; choosing a study design; translating questions of clinical interest into measurable exposures and outcomes; choosing patients for study, including deciding whether a comparison group is needed; determining where data can be found; and deciding how many patients need to be studied and for how long. Once these key design issues have been settled, the registry design should be reviewed to evaluate potential sources of bias (systematic error); these should be addressed to the extent that is practical and achievable. The information value of a registry is enhanced by its ability to provide an assessment of the potential for bias and to quantify how this bias could affect the study results.

The specific research questions of interest will guide the registry's design, including the choice of exposures and outcomes to be studied and the definition of the target population (the population to which the findings are meant to apply). The registry population should be designed to approximate the characteristics of the target population as much as possible. The number of study subjects to be recruited and the length of observation (followup) should be planned in accordance with the overall purpose of the registry. The desired study size (in terms of subjects or person-years of observation) is determined by specifying the magnitude of an expected, clinically meaningful effect or the desired precision of effect estimates. Study size determinants are also affected by practicality, cost, and whether or not the registry is intended to support regulatory decisionmaking. Depending on the purpose of the registry, internal, external, or historical comparison groups strengthen the understanding of whether the observed effects are indeed real and in fact different from what would have occurred under other circumstances.

Registry study designs often restrict eligibility for entry to individuals with certain characteristics (e.g., age) to ensure that the registry will have subgroups with sufficient numbers of patients for analysis. Or the registry may use some form of sampling—random selection, systematic sampling, or a haphazard, nonrandom approach—to achieve this end.

Data Elements

The selection of data elements requires balancing such factors as their importance for the integrity of the registry and for the analysis of primary outcomes, their reliability, their contribution to the overall burden for respondents, and the incremental costs associated with their collection. Selection begins with identifying relevant domains. Specific data elements are then selected with consideration for established clinical data standards, common data definitions, and whether patient identifiers will be used. It is important to determine which elements are absolutely necessary and which are desirable but not essential. In choosing measurement scales for the assessment of patient-reported outcomes, it is preferable to use scales that have been appropriately validated, when such tools exist. Once data elements have been selected, a data map should be created, and the data collection tools should be pilot tested. Testing allows assessment of respondent burden, the accuracy and completeness of questions, and potential areas of missing data. Inter-rater agreement for data collection instruments can also be assessed, especially in registries that rely on chart abstraction. Overall, the choice of data elements should be guided by parsimony, validity, and a focus on achieving the registry's purpose.

Use of Patient Reported Outcomes in Registries

Patient reported outcomes (PROs) are reports of health status taken directly from patients without interpretation by clinicians. PROs can provide useful information for registries designed for many purposes, including natural history of disease, quality improvement, effectiveness, and comparative effectiveness. Using PROs raises such questions as when and how often to collect the data, which method or combination of methods should be used (e.g., paper-based, electronic), and which instrument(s) should be used. Many validated instruments and measures are available, such as general assessment scales (e.g., health-related quality of life), disease-specific scales, symptom-specific scales, evaluations of functioning across a variety of domains (e.g., physical, social, emotional), and scales assessing satisfaction with care received. When selecting instruments or measures, it is important to define (1) the population of interest, (2) the outcomes of interest, (3) the intended users of the registry, and (4) the purpose of the registry. Defining these factors will help determine which PROs are useful and appropriate for the study. The validity, reliability, and ability to detect change of the instrument should also be considered. Once PROs

have been selected, the registry should focus on consistency across patients and across sites in how the instruments are administered and how data are entered into the registry.

Data Sources

A single registry may integrate data from various sources. The form, structure, availability, and timeliness of the required data are important considerations. Data sources can be classified as primary or secondary. Primary data are collected by the registry for its direct purposes. Secondary data have been collected by a secondary source for purposes other than the registry, and may not be uniformly structured or validated with the same rigor as the registry's primary data. Sufficient identifiers are necessary to guarantee an accurate match between data from secondary sources and registry patients. Furthermore, it is advisable to obtain a solid understanding of the original purpose of the secondary data, because the way those data were collected and verified or validated will help shape or limit their use in a registry. Common secondary sources of data linked to registries include medical records systems, institutional or organizational databases, administrative health insurance claims data, death and birth records, census databases, and related existing registry databases.

Ethics, Data Ownership, and Privacy

Critical ethical and legal considerations should guide the development and use of patient registries. The Common Rule is the uniform set of regulations on the ethical conduct of human subjects research issued by the Federal agencies that fund such research. Institutions that conduct research agree to comply with the Common Rule for federally funded research, and may opt to apply that rule to all human subjects activities conducted within their facilities or by their employees and agents, regardless of the source of funding. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its implementing regulations (collectively, the Privacy Rule) are the legal protections for the privacy of individually identifiable health information created and maintained by health care providers, health plans, and health care clearinghouses (called "covered entities"). The research purpose of a registry, the status of its developer, and the extent to which registry data are individually identifiable largely determine which regulatory requirements apply. Other important concerns include transparency of activities, oversight, and data ownership. This section focuses solely on U.S. law. Health information is also legally protected in European and some other countries by distinctly different rules.

Informed Consent for Registries

Informed consent for patient registries often raises different issues than informed consent for clinical trials. For example, registries may be used for public health or quality improvement activities, which may not constitute "human subjects research." Registries also may integrate data from multiple electronic sources (e.g., claims data, electronic health records) and may be linked to biobanks. Institutional review boards may approve waivers or alterations of informed consent (e.g., electronic consent, oral consent) for some registries, depending on the purpose and risk to participants. Established registries that undergo a change in scope (e.g., changes in data sharing policies, changes to the protocol, extension of the follow-up period) may need to reconsent patients. When planning informed consent procedures, registry developers should consider several factors, including documentation and format, consent revisions and re-consent, the applicability of regulatory requirements, withdrawal of participants from the study, and the physical and electronic security of patient data and biological specimens.

Protection of Registry Data from Litigation and Other Confidentiality Concerns for Providers, Manufacturers, and Health Plans

As patient registries are increasingly recognized as a valuable data source, questions about privacy and the confidentiality of the data arise, particularly when data are desired for litigation or other judicial or administrative proceedings. In addition to patient data, registries often include private, confidential, and/or proprietary information about providers, manufacturers, and health plans. While significant attention has been paid to protecting the privacy of identifiable patient information, there is no single comprehensive Federal law governing protection of registry data about providers, manufacturers, or health plans. Sources of protection for these data at the Federal level include the Patient Safety and Quality Improvement Act of 2005, the Health and Human Services Certificate of Confidentiality, the Agency for Healthcare Research and Quality Confidentiality Statute, the HIPAA Privacy Rule, the Privacy Act of 1974, the Federal Rules of Evidence and Civil Procedure, the Freedom of Information Act, Quality Improvement Organizations, the Federal Trade Secrets Act, and the Patient Protection and Affordable Care Act. Additional protections are available at the state level through safe harbor and peer review laws. Registry developers should consider this issue during the planning phase and clearly articulate the policies and procedures that the registry will follow in the case of a request for registry data (e.g., from litigation attorneys, regulatory authorities, the press, or members of the public).

Patient and Provider Recruitment and Management

Recruitment and retention of patients as registry participants and providers as registry sites are essential to the success of a registry. Recruitment typically occurs at several levels, including facilities (hospitals, physicians' practices, and pharmacies), providers, and patients. The motivating factors for participation at each level and the factors necessary to achieve retention differ according to the registry. Factors that motivate participation include the perceived relevance, importance, or scientific credibility of the registry, as well as the risks and burdens of participation and any incentives for participation. Because patient and provider recruitment and retention can affect how well a registry represents the target population, well-planned strategies for enrollment and retention are critical. Goals for recruitment, retention, and followup should be explicitly laid out in the registry planning phase, and deviations during the conduct of the registry should be continuously evaluated for their risk of introducing bias.

Data Collection and Quality Assurance

The integrated system for collecting, cleaning, storing, monitoring, reviewing, and reporting on registry data determines the utility of those data for meeting the registry's goals. A broad range of data collection procedures and systems are available. Some are more suitable than others for particular purposes. Critical factors in the ultimate quality of the data include how data elements are structured and defined, how personnel are trained, and how data problems are handled (e.g., missing, out-of range, or logically inconsistent values). Registries may also be required to conform to guidelines or to the standards of specific end users of the data (e.g., 21 Code of Federal Regulations, Part 11). Quality assurance aims to affirm that the data were, in fact, collected in accordance with established procedures and that they meet the requisite standards of quality to accomplish the registry's intended purposes and the intended use of the data.

Requirements for quality assurance should be defined during the registry's inception and creation. Because certain requirements may have significant cost implications, a risk-based approach to developing

a quality assurance plan is recommended. It should be based on identifying the most important or likely sources of error or potential lapses in procedures that may affect the quality of the registry in the context of its intended purpose.

Adverse Event Detection, Processing, and Reporting

The U.S. Food and Drug Administration defines an adverse event (AE) as any untoward medical occurrence in a patient administered a pharmaceutical product, whether or not related to or considered to have a causal relationship with the treatment. AEs are categorized according to the seriousness and, for drugs, the expectedness of the event. Although AE reporting for all marketed products is dependent on the principle of "becoming aware," collection of AE data falls into two categories: those events that are intentionally solicited (meaning data that are part of the uniform collection of information in the registry) and those that are unsolicited (meaning that the AE is volunteered or noted in an unsolicited manner). Determining whether the registry should use a case report form to collect AEs should be based on the scientific importance of the information for evaluating the specified outcomes of interest. Regardless of whether or not AEs constitute outcomes for the registry, it is important for any registry that has direct patient interaction to develop a plan for detecting, processing, and reporting AEs. If the registry receives sponsorship, in whole or in part, from a regulated industry (drugs or devices), the sponsor has mandated reporting requirements, the process for detecting and reporting AEs should be established, and registry personnel should receive training on how to identify AEs and to whom they should be reported. Sponsors of registries designed specifically to meet requirements for surveillance of drug or device safety are encouraged to hold discussions with health authorities about the most appropriate process for reporting serious AEs.

Analysis, Interpretation, and Reporting of Registry Data

Analysis and interpretation of registry data begin with answering a series of core questions: Who was studied, and how were they chosen for study? How were the data collected, edited, and verified, and how were missing data handled? How were the analyses performed? Four populations are of interest in describing who was studied: the target population, the accessible population, the intended population, and the population actually studied (the "actual population"). The representativeness of the actual population to the target population is referred to as generalizability.

Analysis of registry outcomes first requires an analysis of recruitment and retention, of the completeness of data collection, and of data quality. Considerations include an evaluation of losses to followup; completeness for most, if not all, important covariates; and an understanding of how missing data were handled and reported. Analysis of a registry should provide information on the characteristics of the patient population, the exposures of interest, and the endpoints. Descriptive registry studies focus on describing frequency and patterns of various elements in a patient population, whereas analytical studies concentrate on associations between patients or treatment characteristics and health outcomes of interest. A statistical analysis plan describes the analytical plans and statistical techniques that will be used to evaluate the primary and secondary objectives specified in the study plan. Interpretation of registry data should be provided so that the conclusions can be understood in the appropriate context and any lessons from the registry can be applied to the target population and used to improve patient care and outcomes.

Modifying and Stopping Registries

Most, if not all registries, should undergo periodic critical evaluation by key stakeholders to ensure that the objectives are being met. When registry objectives are no longer being met or when clinical or other changes affect the registry (e.g., changes in treatment practices, the introduction of a new therapy), the registry may need to be adapted, or the registry may stop collecting new data. Many registries will undergo a modification or transition at some point in their lifecycle, and these changes will vary in scope and size. A major registry transition is a change in the purpose, stakeholders, and/or technology platform of the registry that has a substantive impact on the ongoing conduct of the registry. Considerations for the transition of a registry are similar to those for starting a registry, but transitions can also present some unique challenges. It is important to select a leadership team that will carefully plan and implement the transition and consider the impacts of the planned changes (e.g., legal and ethical issues, technology, and data analysis). The transition team should also be prepared to handle unplanned or exigent circumstances that may arise during the transition and modify the project plan accordingly. Open, ongoing communication between the project team, stakeholders, participants, and other resources is key to conducting a successful transition.

A registry may stop collecting new data because it has fulfilled its original purpose, is unable to fulfill its purpose, is no longer relevant, or is unable to maintain sufficient funding, staffing, or other support. If an open-ended registry is planned, reasonable goals should be set for data quality, study enrollment, and the amount of information needed to address specific endpoints of interest which will inform the decision if and when to end the registry.

Interfacing Registries and Electronic Health Records

Achieving interoperability between electronic health records (EHRs) and registries will be increasingly important as adoption of EHRs and the use of patient registries for many purposes both grow significantly. Such interoperability should be based on open standards that enable any willing provider to interface with any applicable registry without requiring customization or permission from the EHR vendor. Interoperability for health information systems requires accurate and consistent data exchange and use of the information that has been exchanged. Syntactic interoperability (the ability to exchange data) and semantic interoperability (the ability to understand the exchanged data) are the core constructs of interoperability and must be present in order for EHRs and registries to share data successfully. Full interoperability is unlikely to be achieved for some time. The successive development, testing, and adoption of open standard building blocks (e.g., the Healthcare Information Technology Standards Panel's HITSP TP-50) is a pragmatic approach toward incrementally advancing interoperability while providing real benefits today. Care must be taken to ensure that integration efforts comply with legal and regulatory requirements for the protection of patient privacy.

Linking Registry Data with Other Data Sources to Support New Studies

Registry data may be linked to other data sources (e.g., administrative data sources, other registries) to examine questions that cannot be addressed using the registry data alone. Two equally weighted and important sets of questions must be addressed in the data linkage planning process: (1) What is a feasible technical approach to linking the data? (2) Is linkage legally feasible under the permissions, terms, and conditions that applied to the original compilations of each dataset? Many statistical techniques for linking records exist (e.g., deterministic matching, probabilistic matching); the choice of a technique should be guided by the types of data available. Linkage projects should include plans for managing

common issues (e.g., records that exist in only one database and variations in units of measure). In addition, it is important to understand that linkage of de-identified data may result in accidental re-identification. Risks of re-identification vary depending on the variables used, and should be managed with guidance from legal and statistical experts to minimize risk and ensure compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the Common Rule, and other legal and regulatory requirements.

Managing Patient Identity across Data Sources

As new technologies emerge to manage electronic health care data and create new opportunities for data linkage, patient identity management (PIM) strategies and standards grow increasingly important. If shared patient identifiers exist between two data sources, data can be linked using a unique patient identifier (UPI), such as a medical record number. The concept of a universal UPI has been the subject of debate for some time. Some view UPIs as a tool to reduce administrative workload and facilitate the exchange of electronic data, while others raise serious concerns about the privacy and protection of patient-identifiable information. These concerns have halted efforts to implement universal UPIs in the U.S. to date. As a result, common PIM practices in the U.S. include algorithms and other statistical methods to link and combine data when no shared patient identifiers are present. However, with no standardized PIM practices in place, methods can vary widely, making it difficult to ensure the accuracy and effectiveness of data linkage techniques.

Analysis of Linked Registry Datasets

Retrospective database studies are studies that use data collected for a primary purpose other than research (e.g., administrative databases) or collected for specific research objectives but used to support secondary studies focused on different objectives. These studies have yielded substantial information on the incidence, prevalence, and outcomes of many diseases and can be used to generate a rapid response to emerging research questions. However, these studies require special considerations related to conduct and interpretation because of the possibility of producing biased or invalid results. Challenges faced by retrospective database studies include inaccurate measurement of exposures, outcomes, and confounders and overweighting of results because of the large study population. To avoid these pitfalls, it is important to clearly define the study objective, patient population, and potential confounders and modifiers. Researchers must also understand the conditions under which the data were collected originally.

Use of Registries for Product Safety Assessment

Whether as part of a postmarketing requirement or out of a desire to supplement spontaneous reporting, prospective product and disease registries are also increasingly being considered as resources for examining unresolved safety issues and/or as tools for proactive risk assessment in the postapproval setting. Registries can be valuable tools for evaluating product safety, although they are only one of many approaches to safety assessments. When designing a registry for the purposes of safety, the size of the registry, the enrolled population, and the duration of followup are all critical characteristics to ensure validity of the inferences made based on the data collected. Consideration in the design phase must also be given to other recognized aspects of product use in the real world (e.g., switching therapies during followup, use of multiple products in combination or in sequence, dose effects, delayed effects, and patient compliance).

Registries designed for safety assessment purposes should also formulate a plan that ensures that appropriate information will reach the right stakeholders (through reporting either to the manufacturer or directly to the regulator) in a timely manner. Stakeholders include patients, clinicians, providers, product manufacturers and authorization holders, and payers such as private, State, and national insurers. Registries not designed specifically for safety assessment purposes should, at a minimum, ensure that standard reporting mechanisms for adverse event information are described in the registry's standard operating procedures and are made clear to investigators.

Rare Disease Registries

A rare disease registry can be a valuable tool for increasing understanding of the disease and supporting the development of treatment protocols and therapies. Typical goals of a rare disease registry include generating knowledge around the natural history, evolution, risk, and outcomes of a specific disease; supporting research on genetic, molecular, and physiological basis of a disease; establishing a patient base for evaluating drug, medical devices, and orphan products; and connecting affected patients, families and clinicians. Many stakeholders often play an important role in rare disease registries. Stakeholders may include patient advocacy groups, regulatory, funding, and public health agencies, clinicians, scientists, industry, payers, and individuals and families. Because of the limited patient population, rare disease registries face unique planning and design challenges. For example, little information may be available on the disease to guide development of a research plan, and diagnostic criteria may be complex or evolving. Disease-specific patient reported outcome measures may not be available. Long-term (even lifelong) follow-up may be needed. Due to these challenges, rare disease registries may need to adapt and change over time as knowledge increases or treatments become available. Retention of patients and providers can also be difficult over the duration of the registry, and registry developers should monitor followup rates over time to identify potential issues. Clear policies for governance, data access, and publications should be developed, particularly if multiple stakeholders are involved.

Pregnancy Registries

A pregnancy exposure registry is an observational prospective cohort of women receiving a biopharmaceutical product(s) of interest as part of their routine clinical care who are enrolled voluntarily during gestation, before outcomes can be known. Participants are followed until the end of pregnancy or longer to systematically collect information on specific pregnancy outcomes and evaluate their frequency relative to a scientifically valid reference population(s). While pregnancy registries are an efficient method for evaluating the effects of medications used during pregnancy, they present unique challenges related to patient recruitment and retention, choosing reference or comparator groups, mitigating bias, and generalizability of registry results. Analysis and interpretation of data from pregnancy registries also requires careful consideration. Because specific birth defects are rare events, pregnancy registries usually do not have sufficient sample size/power to evaluate increased risks for specific defects unless the relative risks are quite large. Most registries compare the overall proportion of all major defects combined in the exposed group to the overall proportion in the reference group.

Quality Improvement Registries

Quality improvement (QI) registries use systematic data collection and other QI tools to improve the quality of care on the local, regional, or national level. In a QI registry, patients are either exposed to a particular health service (e.g., a procedure registry), or they have a disease/condition that is tracked over time through multiple health care providers and services. Most of the steps for planning a QI registry are

similar to the steps used for other types of registries, with two major differences. First, the identification of active, engaged participants, often called "champions" is critical for the early success of the registry. Second, the registry must collect actionable information that can be used to modify behaviors, processes, or systems of care. Actionable information is typically presented to providers in the form of process of care or quality measures. The selection of these measures requires balancing the goals of the registry with the desire to meet other needs for providers. In the design phase, QI registries can use the process of care or quality measures to drive the selection of data elements. Because many data elements collected in QI registries are often collected for other purposes (e.g., claims, medical records), integration with other data sources may be important for encouraging participation. Motivations for participation often differ from other types of registries, and incentives for participation focus on QI (e.g., recognition programs, QI tools, and benchmarking reports). Reporting information is also an important component of QI registries. Registries may report blinded or unblinded data at the individual patient, provider, or institution level. Lastly, QI registries must be able to adapt to new evidence and improvements in care over time, and they may face questions from institutional review boards that are less familiar with these types of registries.

Registries for Medical Devices

Medical device registries are an increasingly important tool for capturing patients' experience with medical devices throughout the device lifecycle. Registries help to bridge the gap between device performance in clinical trial settings and in routine practice. However, the unique features of medical devices require special consideration when developing a registry. Regulations and approval guidelines for medical devices differ greatly from those for drugs. Compared to drugs, device technologies tend to see more rapid change over shorter amounts of time, and device registries must adapt to these changes. The current lack of unique device identifiers is also challenging, although efforts are underway to create unique device identifiers. In many cases, multiple devices are used, and devices may be used in combination with a drug component, further complicating efforts to examine safety and effectiveness. In addition, providers may have different levels of experience with the device, which may affect patient outcomes (especially with implantable devices). Medical device registries should attempt to classify all parts of a device with as much identifying information as possible, and many registries collect information on provider training and experience as well. An emerging trend is the ability for medical devices to transmit data directly to an electronic health record or registry. This new technology may reduce the burden of data entry for registries and increase the timeliness of registry data.

Public-Private Partnerships

A public-private partnership (PPP) refers to any partnership in which one entity is a public agency (e.g., a government entity) and the other entity is a private organization. The use of PPPs as a means to develop patient registries has increased in recent years, in part because of a growing interest from governments and payers in using registry data to make decisions about approval, coverage, and public health needs. Many models for PPPs exist. For example, a PPP may involve a partnership with Federal agencies and academia, health agencies from several countries and industry, or professional associations and public payers. During the planning phase of a PPP, it is important to define clear, transparent plans for governance, with documented roles for each stakeholder. Formal policies for analyses, publications, and data sharing are also critical, as are plans for managing conflicts of interest. During the operational phase, PPPs should focus on consistent communication with stakeholders to maintain interest. PPP registries are more likely to succeed if they have clear, agreed-upon goals; explicit roles and responsibilities for each

stakeholder; strong leaders who are respected in the field; consistent data collection and analysis plans; and the flexibility to adapt to changing conditions.

Evaluating Registries

Although registries can provide useful information, there are levels of rigor that enhance validity and make the information from some registries more useful for guiding decisions than the information from others. The term "quality" can be applied to registries to describe the confidence that the design, conduct, and analysis of the registry can be shown to protect against bias and errors in inference—that is, erroneous conclusions drawn from a registry. Although there are limitations to any assessment of quality, a quality component analysis is used both to evaluate high-level factors that may affect results and to differentiate between research quality (which pertains to the scientific process) and evidence quality (which pertains to the data/findings emanating from the research process). Quality components are classified as either "basic elements of good practice," which can be viewed as a checklist that should be considered for all patient registries, or as "potential enhancements to good practice," which may strengthen the information value in particular circumstances. The results of such an evaluation should be considered in the context of the disease area(s), the type of registry, and the purpose of the registry, and should also take into account feasibility and affordability.

Section I. Creating Registries

Chapter 1. Patient Registries

1. Introduction

The purpose of this document is to serve as a guide for the design and use of patient registries for scientific, clinical, and health policy purposes. Properly designed and executed, patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness. This user's guide primarily focuses on practical design and operational issues, evaluation principles, and best practices. Where topics are well covered in other materials, references and/or links are provided. The goal of this document is to provide stakeholders in both the public and private sectors with information that they can use to guide the design and implementation of patient registries, the analysis and interpretation of data from patient registries, and the evaluation of the quality of a registry or one of its components. Where useful, case examples have been incorporated to illustrate particular points or challenges.

The term registry[1] is defined both as the act of recording or registering and as the record or entry itself. Therefore, "registries" can refer to both programs that collect and store data and the records that are so created.

The term *patient registry* is generally used to distinguish registries focused on health information from other record sets, but there is no consistent definition in current use. E. M. Brooke, in a 1974 publication of the World Health Organization, further delineated registries in health information systems as "a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a predetermined purpose."[2]

The National Committee on Vital and Health Statistics[3] describes registries used for a broad range of purposes in public health and medicine as "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects."

Other terms also used to refer to patient registries include clinical registries, clinical data registries, disease registries, and outcomes registries.[4,5]

This user's guide focuses on patient registries that are used for evaluating patient outcomes. It is not intended to address several other types or uses for registries (although many of the principles may be applicable), such as geographically based population registries (not based on a disease, condition, or exposure); registries created for public health reporting without tracking outcomes (e.g., vaccine registries); or listing registries that are used solely to identify patients with particular diseases in clinical practices but are not used for evaluating outcomes. This user's guide is also not intended to address the wide range of studies that utilize secondary analyses of data collected for other purposes.

Many of these other types of registries are included in the Registry of Patient Registries (RoPR) effort. The RoPR, which is discussed further below, is a central listing of patient registries designed to improve transparency and reduce redundancy in registry-based research. Inclusion of all types of patient registries is important to achieve the RoPR's goals, and the system therefore defines patient registries broadly.

In contrast to the RoPR, this user's guide focuses on the subset of patient registries used for evaluating patient outcomes. This user's guide uses the following definitions for registries designed for evaluating patient outcomes:

- A *patient registry* is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.
- The *patient registry* database describes a file (or files) derived from the registry.

Based on these definitions, the user's guide focuses on patient registries in which the following are true (although exceptions may apply):

- The data are collected in a naturalistic manner, such that the management of patients is determined by the caregiver and patient together and not by the registry protocol.
- The registry is designed to fulfill specific purposes, and these purposes are defined before collecting and analyzing the data. In other words, the data collection is purpose driven rather than the purpose being data driven (meaning limited to or derived from what is already available in an existing dataset).
- The registry captures data elements with specific and consistent data definitions.
- The data are collected in a uniform manner for every patient. This consideration refers to both the types of data and the frequency of their collection.
- The data collected include data derived from and reflective of the clinical status of the patient (e.g., history, examination, laboratory test, or patient-reported data). Registries include the types of data that clinicians would use for the diagnosis and management of patients.
- At least one element of registry data collection is active, meaning that some data are collected specifically for the purpose of the registry (usually collected from the patient or clinician) rather than inferred from sources that are collected for another purpose (administrative, billing, pharmacy databases, etc.). This definition does not exclude situations where registry data collection is a specific, but not the exclusive, reason data are being collected, such as might be envisioned with future uses of electronic health records, as described in Chapter 15. This definition also does not exclude the incorporation of other data sources, as discussed in Chapter 6. Registries can be enriched by linkage with extant databases (e.g., to determine deaths and other outcomes or to assess pharmacy use or resource utilization), as discussed in Chapter 16.

Data from patient registries are generally used for studies that address the purpose for which the registry was created. In some respects, such as the collection of detailed clinical and longitudinal follow-up data, studies derived from the patient registries described in this user's guide resemble traditional observational cohort studies. Beyond traditional cohort studies, however, some registry-based studies may be more flexible in that the scope and focus of the data collection activity of the registry may be adapted over time

to address additional needs. For example, new studies, such as cluster-randomized studies or case-control studies, may be nested within an ongoing registry, and the database derived from the registry may be used to support secondary studies, such as studies that link the registry database with other data sources to explore new questions.

2. Current Uses for Patient Registries

A patient registry can be a powerful tool to observe the course of disease; to understand variations in treatment and outcomes; to examine factors that influence prognosis and quality of life; to describe care patterns, including appropriateness of care and disparities in the delivery of care; to assess effectiveness; to monitor safety and harm; and to measure quality of care. Through functionalities such as feedback of data, registries are also being used to study quality improvement.[6]

Different stakeholders perceive and may benefit from the value of registries in different ways. For example, for a clinician, registries can collect data about disease presentation and outcomes on large numbers of patients rapidly, thereby producing a real-world picture of disease, current treatment practices, and outcomes. For a physician organization, a registry might provide data that can be used to assess the degree to which clinicians are managing a disease in accordance with evidence-based guidelines, focus attention on specific aspects of a particular disease that might otherwise be overlooked, or provide data for clinicians to compare themselves with their peers.[7] For patients and patient advocacy organizations, a registry may increase understanding of the natural history of a disease, contribute to the development of treatment guidelines, or facilitate research on treatments.[8,9] From a payer's perspective, registries can provide detailed information from large numbers of patients on how procedures, devices, or pharmaceuticals are actually used and on their effectiveness in different populations. This information may be useful for determining coverage policies.[10] For a drug or device manufacturer, a registry-based study might demonstrate the performance of a product in the real world, meet a postmarketing commitment or requirement,[11] develop hypotheses, or identify patient populations that will be useful for product development, clinical trials design, and patient recruitment. The U.S. Food and Drug Administration (FDA) has noted that "through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate the factors that affect the risk of adverse outcomes such as dose, timing of exposure, or patient characteristics."[12]

The use of patient registries varies by priority condition, with cancer and cardiovascular disease having a large number of registries and areas such as developmental delays or dementia, far fewer. Overall, the use of patient registries appears to be active and growing. For example, a review of ClinicalTrials.gov in the area of cancer reveals over 270 large (more than 2,000 patients) observational studies that would meet the criteria for a patient registry. Of these studies, 4 have more than 100,000 patients, and 27 have more than 10,000. In some cases, the drivers for these registries have been Federal stakeholders. For example, since 2005, the FDA Center for Devices and Radiological Health has called for some 160 postapproval studies, many of which use new or existing registries to study the real-world effectiveness of specific devices in community practice.[13] The establishment of the RoPR in 2012 by the Agency for Healthcare Research and Quality (AHRQ) in collaboration with the National Library of Medicine provides a new resource for tracking registry development and use by condition, purpose, type and multiple other factors.[14]

2.1. Evaluating Patient Outcomes

Studies from patient registries and randomized controlled trials (RCTs) have important and complementary roles in evaluating patient outcomes.[15] Ideally, patient registries collect data in a comprehensive manner (with few excluded patients) and therefore produce outcome results that may be generalizable to a wide range of patients. They also evaluate care as it is actually provided, because care is not assigned, determined, or even recommended by a protocol. As a result, the outcomes reported may be more representative of what is achieved in real-world practice. Patient registries also offer the ability to evaluate patient outcomes when clinical trials are not practical (e.g., very rare diseases), and they may be the only option when clinical trials are not ethically acceptable. They are a powerful tool when RCTs are difficult to conduct, such as in surgery or when very long-term outcomes are desired.

RCTs are controlled experiments designed to test hypotheses that can ultimately be applied to real-world care. Because RCTs are often conducted under strict constraints, with detailed inclusion and exclusion criteria (and the need for subjects who are willing to be randomized), they are sometimes limited in their generalizability. If RCTs are not generalizable to the populations to which the information will be applied, they may not be sufficiently informative for decisionmaking. Conversely, patient registries that observe real-world clinical practice may collect all of the information needed to assess patient outcomes in a generalizable way, but interpreting this information correctly requires analytic methodology geared to address the potential sources of bias that challenge observational studies. Interpreting patient registry data also requires checks of internal validity and sometimes the use of external data sources to validate key assumptions (such as comparing the key characteristics of registry participants with external sources in order to demonstrate the comparability of registry participants with the ultimate reference population). Patient registries, RCTs, other study designs, and other data sources should all be considered tools in the toolbox for evidence development, each with its own advantages and limitations.[16]

2.2. Hierarchies of Evidence

One question that arises in a discussion of this type is where to place studies derived from patient registries within the hierarchies of evidence that are frequently used in developing guidelines or decisionmaking. While the definition of patient registry used in this user's guide is intentionally broad, the parameters of quality described in Chapter 25 are intended to help the user evaluate and identify registries that are sufficiently rigorous observational studies for use as evidence in decisionmaking. Many registries are, or include, high-quality studies of cohorts designed to address a specific problem and hypothesis. Still, even the most rigorously conducted registries, like prospective observational studies, are traditionally placed in a subordinate position to RCTs in some commonly used hierarchies, although equal to RCTs in others.[17,18,19] Debate continues in the evidence community regarding these traditional methods of grading levels of evidence, their underlying assumptions, their shortcomings in assessing certain types of evidence (e.g., benefit vs. harm), and their interscale consistency in evaluating the same evidence.[16,20,21]

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group has proposed a more robust approach that addresses some of the decisionmaking issues described in this user's guide. As noted by the GRADE collaborators:

> [R]andomised trials are not always feasible and, in some instances, observational studies may provide better evidence, as is generally the case for rare adverse effects. Moreover, the results of

> randomised trials may not always be applicable– for example, if the participants are highly selected and motivated relative to the population of interest. It is therefore essential to consider study quality, the consistency of results across studies, and the directness of the evidence, as well as the appropriateness of the study design.[22]

AHRQ has also developed a guidance system for grading the strength of evidence that recommends a careful assessment of the potential value of observational studies. The guidance, which is designed to support the systematic reviews conducted by the Evidence-based Practice Center (EPC) program, is conceptually similar to the GRADE system.[23] When using the AHRQ approach, reviewers typically give evidence from observational studies a low starting grade and evidence from RCTs a high starting grade. These initial grades can then be raised or lowered depending on the strength of the five required evidence domains (study limitations, directness, consistency, precision, and reporting bias).[24] For example, the reviewers may find that observational studies are particularly relevant for some systematic review questions. The report notes:

> EPCs may act on the judgment that, for certain outcomes such as harms, observational studies have less risk of bias than do RCTs or that the available RCTs have a substantial risk of bias. In such instances, the EPC may move up the initial grade for strength of evidence based on observational studies to moderate or move down the initial rating based on RCTs to moderate.[23]

Reviewers may also raise or lower evidence grades based on a secondary set of domains (dose-response association, existence of confounding that would diminish an observed effect, and strength of association). These secondary domains supplement the required domains and are used when relevant to the systematic review question. The authors note that the secondary domains "may increase strength of evidence and are especially relevant for observational studies where one may begin with a lower overall strength of evidence grade based on study limitations."[23]

As the methods for grading evidence for different purposes continue to evolve, this user's guide can serve as a guide to help such evaluators understand study quality and identify well-designed registries. Beyond the evidence hierarchy debate, users of evidence understand the value of registries for providing complementary information that can extend the results of clinical trials to populations not studied in those trials, for demonstrating the real-world effects of treatments outside of the research setting and potentially in large subsets of affected patients, and for providing long-term followup when such data are not available from clinical trials.

2.2.1. Defining Patient Outcomes

The focus of this user's guide is the use of registries to evaluate patient outcomes. An outcome may be thought of as an end result of a particular health care practice or intervention. According to the Agency for Healthcare Research and Quality, end results include effects that people experience and about which they care.[25] The National Cancer Institute further clarifies that "final" endpoints are those that matter to decisionmakers: patients, providers, private payers, government agencies, accrediting organizations, or society.[26,27] Examples of these outcomes include biomedical outcomes, such as survival and disease-free survival, health-related quality of life, satisfaction with care, and economic burden.[28] Although final endpoints are ultimately what matter, it is sometimes more practical when creating registries to collect intermediate outcomes (such as whether processes or guidelines were followed) and clinical outcomes (such as whether a tumor regressed or recurred) that predict success in improving final endpoints.

In *Crossing the Quality Chasm*,[29] the Institute of Medicine (IOM) describes the six guiding aims of health care as providing care that is safe, effective, efficient, patient-centered, timely, and equitable. (The last three aims focus on the delivery and quality of care.) While these aims are not outcomes per se, they generally describe the dimensions of results that matter to decisionmakers in the use of a health care product or service: Is it safe? Does it produce greater benefit than harm? Is it clinically effective? Does it produce the desired effect in real-world practice? Does the right patient receive the right therapy or service at the right time? Is it cost-effective or efficient? Does it produce the desired effect at a reasonable cost relative to other potential expenditures? Is it patient oriented, timely, and equitable? Most of the patient outcomes that registries evaluate reflect one or more of the IOM guiding aims. For example, a patient presenting with an ischemic stroke to an emergency room has a finite window of opportunity to receive a thrombolytic drug, and the patient outcome, whether or not the patient achieves full recovery, is dependent not only on the product dissolving the clot but also the timeliness of its delivery.[30,31]

2.2.2. Purposes of Registries

As discussed throughout this user's guide, registries should be designed and evaluated with respect to their intended purpose(s). Registry purposes can be broadly described in terms of patient outcomes. While there are a number of potential purposes for registries, this handbook primarily discusses four major purposes: describing the natural history of disease, determining clinical and/or cost-effectiveness, assessing safety or harm, and measuring or improving quality of care. Other purposes of patient registries mentioned but not discussed in detail in this user's guide are for public health surveillance and disease control. An extensive body of literature from the last half century of experience with cancer and other disease surveillance registries is available.

2.2.3. Describing Natural History of Disease

Registries may be established to evaluate the natural history of a disease, meaning its characteristics, management, and outcomes with and/or without treatment. The natural history may be variable across different groups or geographic regions, and it often changes over time. In many cases, the natural histories of diseases are not well described. Furthermore, the natural histories of diseases may change after the introduction of certain therapies. As an example, patients with rare diseases, such as the lysosomal storage diseases, who did not previously survive to their twenties, may now be entering their fourth and fifth decades of life, and this uncharted natural history is being first described through a registry.[32] The role of registries in rare diseases is explored in Chapter 20.

2.2.4. Determining Effectiveness

Registries may be developed to determine clinical effectiveness or cost-effectiveness in real-world clinical practice. Multiple studies have demonstrated disparities between the results of clinical trials and results in actual clinical practice.[33,34] Furthermore, efficacy in a clinical trial for a well-defined population may not be generalizable to other populations or subgroups of interest. As an example, many important heart failure trials have focused on a predominantly white male population with a mean age of approximately 60 years, whereas actual heart failure patients are older, more diverse, and have a higher mortality rate than the patients in these trials.[35] Similarly, underrepresentation of older patients has been reported in clinical trials of 15 different types of cancer (e.g., studies with only 25 percent of patients age 65 years and over, while the expected rate is greater than 60 percent).[36] Data from registries have been used to fill these gaps for decisionmakers. For example, the FDA used the American Academy of Ophthalmology's intraocular lens registry to expand the label for intraocular lenses to younger patients.[37]

Registries may also be particularly useful for tracking effectiveness outcomes for a longer period than is typically feasible with clinical trials. For example, some growth hormone registries have tracked children well into adulthood.

In addition to clinical effectiveness, registries can be used to assess cost-effectiveness. Registries can be designed to collect cost data and effectiveness data for use in modeling cost-effectiveness.[38] Cost-effectiveness is a means to describe the comparative value of a health care product or service in terms of its ability to achieve a desired outcome for a given unit of resources.[39] A cost-effectiveness analysis examines the incremental benefit of a particular intervention and the costs associated with achieving that benefit. Cost-effectiveness studies compare costs with clinical outcomes measured in units such as life expectancy or disease-free periods. Cost-utility studies compare costs with outcomes adjusted for quality of life (utility), such as quality-adjusted life years (QALYs). Utilities allow comparisons to be made across conditions because the measurement is not disease specific.[40] It should be noted that for both clinical effectiveness and cost-effectiveness, differences between treatments are indirect and must be inferred from data analysis, simulation modeling, or some mixture.

With improvement in methodologies for using observational research for comparative effectiveness research (CER), including better methods for managing bias and better understanding of the limitations,[41] there is both increasing interest and investment in registries for CER across a number of stakeholders. Reports from the IOM and the Congressional Budget Office in 2007 cited the importance of patient registries in developing comparative effectiveness evidence.[42,43] The Federal Coordinating Council for Comparative Effectiveness Research in its Report to the President and the Congress (June 30, 2009), defined CER as "the conduct and synthesis of research comparing benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in 'real world' settings."[44] The report specifically identifies patient registries as a core component of CER data infrastructure. More recently, the newly formed Patient-Centered Outcomes Research Institute (PCORI) has identified registries as an important potential source of data to support patient-centered outcomes research (PCOR). PCOR "assesses the benefits and harms of preventive, diagnostic, therapeutic, palliative, or health delivery system interventions to inform decision making, highlighting comparisons and outcomes that matter to people; is inclusive of an individual's preferences, autonomy and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health related quality of life; incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination; and

investigates (or may investigate) optimizing outcomes while addressing burden to individuals, availability of services, technology, and personnel, and other stakeholder perspectives."[45] Similar to CER, registries are expected play an important role in this new area of research in part because of their ability to provide information on 'real world' settings and broad patient populations. PCORI included minimum standards for the use of registries for PCOR in the Methodology Report.[46] While some registries are designed explicitly to examine questions of comparative effectiveness or patient-centered outcomes research, many others are designed for different objectives yet still collect data that are useful for these analyses. Registries that were not explicitly designed for CER or PCOR may need to be augmented or linked to other data sources; for example, to obtain long-term outcomes data in the case of an in-hospital registry using linkage to claims data to evaluate blood pressure medications.[47]

2.2.5. Measuring or Monitoring Safety and Harm

Registries may be created to assess safety vs. harm. Safety here refers to the concept of being free from danger or hazard. One goal of registries in this context may be to quantify risk or to attribute it properly. Broadly speaking, patient registries can serve as an active surveillance system for the occurrence of unexpected or harmful events for products and services. Such events may range from patient complaints about minor side effects to severe adverse events such as fatal drug reactions or patient falls in the hospital.

Patient registries offer multiple advantages for active surveillance. First, the current practice of spontaneous reporting of adverse events relies on a nonsystematic recognition of an adverse event by a clinician and the clinician's active effort to make a report to manufacturers and health authorities. Second, these events are generally reported without a denominator (i.e., the exposed or treated population), and therefore an incidence rate is difficult to determine. Because patient registries can provide systematic data on adverse events and the incidence of these events, they are being used with increasing frequency in the areas of health care products and services. The role of registries in monitoring product safety is discussed in more detail in Chapter 19.

2.2.6. Measuring Quality

Registries may be created to measure quality of care. The IOM defines quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." Quality-focused registries are being used increasingly to assess differences between providers or patient populations based on performance measures that compare treatments provided or outcomes achieved with "gold standards" (e.g., evidence-based guidelines) or comparative benchmarks for specific health outcomes (e.g., risk-adjusted survival or infection rates). Such programs may be used to identify disparities in access to care, demonstrate opportunities for improvement, establish differentials for payment by third parties, or provide transparency through public reporting. There are multiple examples of such differences in treatment and outcomes of patients in a range of disease areas.[48,49,50,51,52,53] Quality improvement registries are described further in Chapter 22.

2.2.7. Multiple Purposes

Many registries will be developed to serve more than one of these purposes. Registries developed for one purpose may also be modified to serve additional purposes as the research, practice, or policy environment changes. While registries often serve more than one purpose, their original or primary purpose generally guides their design and, as a result, more care is needed in evaluating results for secondary or additional purposes.

3. Taxonomy for Patient Registries

Even limited to the definitions described above, the breadth of studies that might be included as patient registries is large. Patients in a registry are typically selected based on a particular disease, condition (e.g., a risk factor), or exposure. This user's guide utilizes these common selection criteria to develop a taxonomy or classification based on how the populations for registries are defined. Three general categories with multiple subcategories and combinations account for the majority of registries that are developed for evaluating patient outcomes. These categories include observational studies in which the patient has had an exposure to a product or service, has a particular disease or condition, or various combinations thereof.

3.1. Product Registries

In the case of a product registry, the patient is exposed to a health care product, such as a drug or a device. The exposure may be brief, as in a single dose of a pharmaceutical product, or extended, as in an implanted device or chronic usage of a medication. Device registries may include all, or a subset, of patients who receive the device. A registry for all patients who receive an implantable cardioverter defibrillator, a registry of patients with hip prostheses, or a registry of patients who wear contact lenses are all examples of device registries. Biopharmaceutical product registries similarly have several archetypes, which may include all, or subsets, of patients who receive the biopharmaceutical product. For example, the British Society for Rheumatology established a national registry of patients on biologic therapy.[54] Again, the duration of exposure may range from a single event to a lifetime of use. Eligibility for the registry includes the requirement that the patient received the product or class of products (e.g., COX-2 inhibitors). In some cases, such registries are mandated by public health authorities to ensure safe use of medications. Examples include registries for thalidomide, clozapine, and isotretinoin. Pregnancy registries represent a separate class of biopharmaceutical product registries that focus on possible exposures during pregnancy and the neonatal consequences. The FDA has a specific guidance focused on pregnancy exposure registries, which is available at http://www.fda.gov/CbER/gdlns/pregexp.htm. This guidance uses the term "pregnancy exposure registry" to refer to "a prospective observational study that actively collects information on medical product exposure during pregnancy and associated pregnancy outcomes." Pregnancy registries are discussed in more detail in Chapter 21.

3.2. Health Services Registries

In the context of evaluating patient outcomes, another type of exposure that can be used to define registries is exposure to a health care service. Health care services that may be utilized to define inclusion in a registry include individual clinical encounters, such as office visits or hospitalizations, procedures, or full episodes of care. Examples include registries enrolling patients undergoing a procedure (e.g., carotid endarterectomy, appendectomy, or primary coronary intervention) or admitted to a hospital for a particular diagnosis (e.g., community-acquired pneumonia). In these registries, one purpose of the registry is to evaluate the health care service with respect to the outcomes. Health care service registries are sometimes used to evaluate the processes and outcomes of care for quality measurement purposes (e.g., Get With The Guidelines® of the American Heart Association, National Surgical Quality Improvement Program of the Department of Veterans Affairs and the American College of Surgeons).

3.3. Disease or Condition Registries

Disease or condition registries use the state of a particular disease or condition as the inclusion criterion. In disease or condition registries, the patient may always have the disease (e.g., a rare disease such as cystic fibrosis or Pompe disease, or a chronic illness such as heart failure, diabetes, or end-stage renal disease) or may have the disease or condition for a more limited period of time (e.g., infectious diseases, some cancers, obesity). These registries typically enroll the patient at the time of a routine health care service, although patients also can be enrolled through voluntary self-identification processes that do not depend on utilization of health care services (such as Internet recruiting of volunteers). In other disease registries, the patient has an underlying disease or condition, such as atherosclerotic disease, but is enrolled only at the time of an acute event or exacerbation, such as hospitalization for a myocardial infarction or ischemic stroke.

3.4. Combinations

Complicating this classification approach is the reality that these categories can be overlapping in many registries. For example, a patient with ischemic heart disease may have an acute myocardial infarction and undergo a primary coronary intervention with placement of a drug-eluting stent and postintervention management with clopidogrel. This patient could be enrolled in an ischemic heart disease registry tracking all patients with this disease over time, a myocardial infarction registry that is collecting data on patients who present to hospitals with acute myocardial infarction (cross-sectional data collection), a primary coronary intervention registry that includes management with and without devices, a coronary artery stent registry limited to ischemic heart disease patients, or a clopidogrel product registry that includes patients undergoing primary coronary interventions.

3.5. Duration of Observation

The duration of the observational period for a registry is also a useful descriptor. Observation periods may be limited to a single episode of care (e.g., a hospital discharge registry for diverticulitis), or they may extend for as long as the lifetime of patients with a chronic disease (e.g., cystic fibrosis or Pompe disease) or patients receiving a novel therapy (e.g., gene therapy). The period of observation or followup depends on the outcomes of interest.

3.6. From Registry Purpose to Design

As will be discussed extensively in this document, the purpose of the registry defines the registry focus (e.g., product vs. disease) and therefore the registry type. A registry created for the purpose of evaluating outcomes of patients receiving a particular coronary artery stent might be designed as a single product registry if, for example, the purpose is to systematically collect adverse event information on the first 10,000 patients receiving the product. However, the registry might alternatively be designed as a health care service registry for primary coronary intervention if a purpose is to collect comparative effectiveness or safety data on other treatments or products within the same registry.

4. Patient Registries and Policy Purposes

In addition to the growth of patient registries for scientific and clinical purposes, registries are receiving increased attention for their potential role in policymaking or decisionmaking.[55,56] As stated earlier, registries may offer a view of real-world health care that is typically inaccessible from clinical trials or other data sources and may provide information on the generalizability of the data from clinical trials to populations not studied in those trials.

The utility of registry data for decisionmaking is related to three factors: the stakeholders, the primary scientific question, and the context. The stakeholders are those associated with the disease or procedure that may be affected from a patient, provider, payer, regulator, or other perspective. The primary scientific question for a registry may relate to effectiveness, safety, or practice patterns. The context includes the scientific context (e.g., previous randomized trials and modeling efforts that help to more precisely define the primary scientific question), as well as the political, regulatory, funding, and other issues that provide the practical parameters around which the registry is developed. In identifying the value of information from registries, it is essential to look at the data with specific reference to the purpose and focus of the registry.

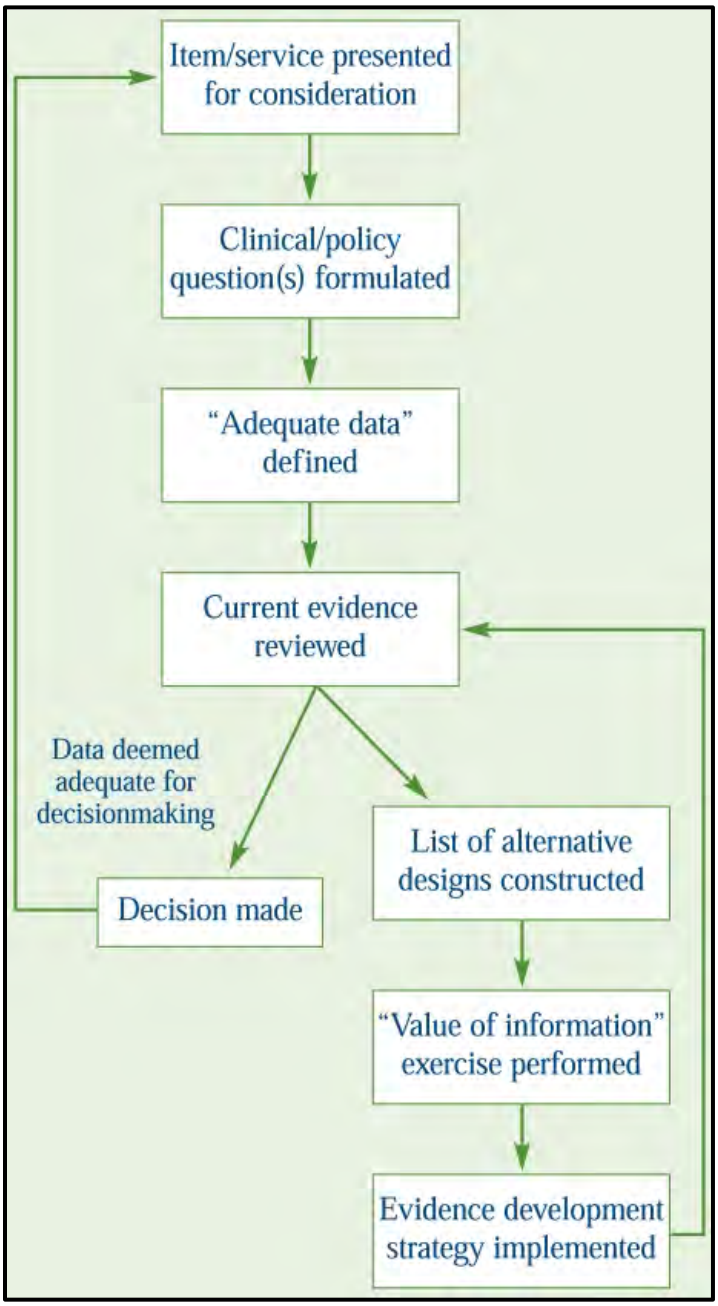
From a policy perspective, there are several scenarios in which the decision to develop a registry may arise. One possible scenario is as follows. An item or service is considered for use. Stakeholders in the decision collaboratively define "adequate data in support of the decision at hand." Here, "adequate data" refers to information of sufficient relevance and quality to permit an informed decision. An evidence development strategy is selected from one of many potential strategies (RCT, practical clinical trial, registry, etc.) based on the quality of the evidence provided by each design, as well as the burden of data collection and the cost that is imposed. This tradeoff of the quality of evidence vs. cost of data collection for each possible design is termed the "value of information" exercise (Figure 1). Registries should be preferred in those circumstances where they provide sufficiently high-quality information for decisionmaking at a sufficiently low cost (relative to other "acceptable" designs).

One set of policy determinations that may be informed by a patient registry centers on the area of payment for items or services. For example, the Centers for Medicare & Medicaid Services (CMS) issued Guidance on National Coverage Determinations With Data Collection as a Condition of Coverage in 2006. That original guidance document (which has undergone subsequent revisions) provided several examples of how data collected in a registry might be used in the context of coverage determinations. As described in the Guidance:

> [T]he purpose of CED [Coverage with Evidence Development] is to generate data on the utilization and impact of the item or service evaluated in the NCD [National Coverage Determination], so that Medicare can a) document the appropriateness of use of that item or service in Medicare beneficiaries under current coverage; b) consider future changes in coverage for the item or service; c) generate clinical information that will improve the evidence base on which providers base their recommendations to Medicare beneficiaries regarding the item or service.[55]

The Guidance provided insight into when registry data may be useful to policymakers. These purposes range from demonstrating that a particular item or service was provided appropriately to patients meeting specific characteristics, to collecting new information that is not available from existing clinical trials. CED based on registries may be especially relevant when current data do not address relevant outcomes for beneficiaries, off-label or unanticipated uses, important patient subgroups, or operator experience or other qualifications. They may also be important when an existing treatment is being reconsidered. (An RCT may not be possible under such circumstances.) Registry-based studies are also being used increasingly in fulfillment of postmarketing commitments and requirements. In many countries, policy determinations on payment rely on cost-effectiveness and cost-utility data and therefore can be informed by registries as well as clinical trials.[57] These data are used and reviewed in a variety of ways. In some countries, there may be a threshold above which a payer is willing to pay for an improvement in patient outcomes.[58] In these scenarios—particularly for rare diseases, when it can be difficult to gather clinical effectiveness data together with quality-of-life data in a utility format—the establishment of disease-specific data registries has been recommended to facilitate the process of technology assessment and improving patient care.[59] In fact, the use of new or existing registries to assess health technology or risk-sharing arrangements is growing in such countries as the United Kingdom, France, Germany, and Australia, and in conditions ranging from bariatric surgery to stroke care.[60,61,62,63,64,65]

Figure 1. Deciding When to Develop a Registry: The "Value of Information" Exercise



Consider the clinical question of carotid endarterectomy surgery for patients with a high degree of stenosis of the carotid artery. Randomized trials, using highly selected patients and surgeons, indicate a benefit of surgery over medical management in the prevention of stroke. However, that benefit may be exquisitely sensitive to the surgical complication rates; a relatively small increase in the rate of surgical complications is enough to make medical management the preferred strategy instead. In addition, the studies of surgical performance in a variety of hospitals may suggest substantial variation in surgical mortality and morbidity for this procedure. In such a case, a registry to evaluate treatment outcomes, adjusted by hospital and surgeon, might be considered to support a policy decision as to when the

procedure should be reimbursed (e.g., only when performed in medical centers resembling those in the various randomized trials, or only by surgeons or facilities with an acceptably low rate of complications).[66]

5. Global Registries

As many stakeholders have international interests in diseases, conditions, and health care products and services, it is not surprising that interest in global patient registries is growing. While some of the specific legal and regulatory discussions in this user's guide are intended for and limited to the United States, most of the concepts and specifics are more broadly applicable to similar activities worldwide. Chapters 7 (ethics, data ownership, and privacy), 9 (protection of registry data), and 12 (adverse event detection, processing, and reporting) are perhaps the most limited in their applicability outside the United States. There may be additional considerations in data element and patient-reported outcome measure selection (Chapters 4 and 5) stemming from differences ranging from medical training to use of local remedies; the types of data sources that are available outside the United States (Chapter 6); the requirements for informed consent (Chapter 8); the issues surrounding clinician and patient recruitment and retention in different health systems and cultures (Chapter 10); specific data collection and management options and complexities (Chapter 11), ranging from available technologies to languages; and specific requirements for mandated pregnancy registries (Chapter 21).

6. Summary

A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical, or policy purpose(s). Studies derived from well-designed and well-performed patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and clinical, comparative, and cost-effectiveness, and can serve a number of evidence development and decisionmaking purposes. In the chapters that follow, this user's guide presents practical design and operational issues, evaluation principles, and good registry practices.

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Chapter 2. Planning a Registry

1. Introduction

There is tremendous variability in size, scope, and resource requirements for registries. Registries may be large or small in terms of numbers of patients or participating sites. They may target rare or common conditions and exposures. They may require the collection of limited or extensive amounts of data, operate for short or long periods of time, and be funded generously or operate with limited financial support. In addition, the scope and focus of a registry may be adapted over time to reach broader or different populations, to assimilate additional data, to focus on or expand to different geographical regions, or to address new research questions. While this degree of flexibility confers enormous potential, registries require good planning in order to be successful.

When planning a registry, it is desirable to follow these initial steps: (1) articulate the purpose of the registry; (2) determine if a registry is an appropriate means to achieve the purpose; (3) identify key stakeholders; and (4) assess the feasibility of a registry.

Once a decision is made to proceed, the next considerations in planning are to (5) build a registry team; (6) establish a governance and oversight plan; (7) define the scope and rigor needed; (8) define the dataset, patient outcomes, and target population; (9) develop a study plan or protocol; and (10) develop a project plan. Of course, the planning for a registry is often not a linear process. Many of the steps described in this chapter occur in parallel.

Registry planners should also recognize the importance of periodic critical evaluations of the registry by key stakeholders to ensure that the objectives are being met. This is particularly important for patient registries that collect data over many years. When registry objectives are no longer being met or when clinical or other changes affect the registry (e.g., changes in treatment practices, the introduction of a new therapy), the registry may need to be adapted, or the registry may stop collecting new data. Registries may undergo a transition or cease collecting new data for many reasons. These considerations are fully discussed in Chapter 14.

The *Guidelines for Good Pharmacoepidemiology Practice* from the International Society of Pharmacoepidemiology is a useful resource for registry planners.[1] The *Updated Guidelines for Evaluating Public Health Surveillance Systems* may also be useful, especially the appendixes, which provide various checklists.[2] A *Guide to the Project Management Body of Knowledge (PMBOK® Guide)* and the GRACE principles for comparative effectiveness (www.graceprinciples.org) may also be a useful resources to registry planners.[3,4]

2. Steps in Planning a Registry

2.1. Articulate the Purpose

One of the first steps in planning a registry is articulating the purpose. Having a clearly defined goal and/or purpose and supporting rationale makes it easier to evaluate whether a registry is the right approach for capturing the information of interest.[5,6] In addition, a clearly defined purpose helps clarify the need for certain data. Conversely, having a clear sense of how the data may be used will help refine

the stated purpose. Attempts to be all inclusive may add cost but not value, resulting in overly burdensome data collection that can reduce quality and erode compliance.

A registry may have a singular purpose or several purposes.[7] In either case, the overall purpose should be translated into specific objectives or questions to be addressed through the registry. This process needs to take into account the interests of those collaborating in the registry and the key audiences to be reached.[8] Clear objectives are essential to define the structure and process of data collection and to ensure that the registry effectively addresses the important questions through the appropriate outcomes analyses. Specific objectives also help the registry to avoid collecting large amounts of data of limited value. The time and resources needed to collect and process data from a registry can be substantial.[9] The identification of a core dataset is essential. The benefits of any data element included in the registry must outweigh the costs of including it.

Establish specific objectives by considering what key questions the registry needs to answer. Critical consideration should be given to defining the key questions in order to evaluate how best to proceed, as these questions will help to establish the type of registry (e.g., single focus or comparative), the data elements to be captured, and the types of analysis to be undertaken. Examples of key, or driving, questions are listed below:

- What is the natural course of a disease, and how does geographic location affect the course?
- Does a treatment lead to long-term benefits or harm, including delayed complications?
- How is disease progression affected by available therapies?
- What are significant predictors of poor outcomes?
- What is the safety profile of a specific therapy?
- Is a specific product or therapy teratogenic?
- How do clinical practices vary, and what are the best predictors of treatment practices?
- Are there disparities in the delivery and/or outcomes of care?
- What characteristics or practices enhance compliance and adherence?
- Do quality improvement programs affect patient outcomes, and, if so, how?
- What process and outcomes metrics should be incorporated to track quality of patient care?
- Should a particular procedure or product be a covered benefit in a particular population?
- Was an intervention program or risk-management activity successful?
- What are the resources used/economic parameters of actual use in typical patients?

2.2. Determine if a Registry Is an Appropriate Means to Achieve the Purpose

Two key questions to consider are whether a registry (or other study) is needed to address the purpose and, if the answer is yes, whether prospective data collection through a registry is an appropriate means of accomplishing the scientific objectives. Every registry developer should consider early in the planning process:

- Do these data already exist?
- If so, are they of sufficient quality to answer the research question?
- Are they accessible, or does an entirely new data collection effort need to be initiated?

For example, could the necessary data be extracted from electronic medical records or administrative health insurance claims data? In such cases, registries might avoid re-collecting data that have already been collected elsewhere and are accessible. Thought should be given to adapting the registry (based on

extant data) and/or linking to other relevant data sources (including "piggybacking" onto other registries). The Registry of Patient Registries (RoPR), developed by the Agency for Healthcare Research and Quality, is a resource for finding patient registries. When the required data have not been sufficiently collected or are not accessible for the desired purpose, it is appropriate to consider creating a new registry.

The next step is to consider whether the purpose would be well served a registry. When making this decision, it is important to fully define the specific research question(s) of interest and to consider the state of current knowledge and gaps in evidence. Other factors that may influence this decision include how broad the target population of interest is, how complex the current treatment patterns are, how long an observational period would be needed to achieve the objective, the scope and variety of treatments used, the approximate amount of funding available to address these objectives, and the urgency of decisions that will be made based on the resulting evidence. Registries may be the most appropriate choice for some research questions. For example, registries are particularly useful in situations where a comprehensive, flexible research design is needed,[10 11] or when the purpose is to discover how a product works in a wide variety of subgroups. (See Section 3.2 for a discussion of research questions appropriate for registries.) Other research questions, such as ones that might be used to petition a regulatory agency for a new indication, will require different approaches, such as traditional randomized controlled trials. In some cases, a hybrid approach, such as a registry that incorporates data collected retrospectively as well as prospectively, will be required. A research strategy, as opposed to a single study, may be necessary to address some research questions. For example, some research questions may require an interventional approach to address concerns about efficacy combined with an observational approach to examine long-term outcomes and quality of life in a broad patient population. When making a decision about study design, it is important to select the approach or combination of approaches that are best able to answer the specific research questions, from both a scientific and practical standpoint. A careful evaluation of the possibilities for data collection and registry design, the degree of certainty required, and the timeframe in which this certainty is expected can help in selecting an appropriate study design.

Historically, there has been a lack of consensus standards for conducting and reporting methods and results for registries. Therefore, registries have been more variable in implementation and have been more difficult to assess for quality than randomized controlled trials. Advances in epidemiological and biostatistical methods have broadened the scope of questions that can be addressed through observational studies such as registries. Stratification, propensity score matching, and risk adjustment are increasingly useful approaches for addressing confounding issues and for creating comparably homogeneous subgroups for analysis within registry datasets, and advances in bias analysis are being used to help interpret results from observational studies such as registries.[12 13 14] (See Chapters 3, 13, and 18.) These techniques may allow registries to be used to support investigations of comparative safety and effectiveness. Following good registry practices, as described in this user's guide, can strengthen scientific rigor. (See Chapter 25.)

2.3. Identify Key Stakeholders

As a means to identifying potential stakeholders, it is important to consider to whom the research questions matter. It is useful to identify these stakeholders at an early stage of the registry planning process, as they may have important input into the type and scope of data to be collected, they may ultimately be users of the data, and/or they may have a key role in disseminating the results of the registry.

One or more parties could be considered stakeholders of the registry. These parties could be as specific as a regulatory agency that will be monitoring postmarketing studies or as broad as the general population, or simply those patients with the conditions of interest. Often, a stakeholder's input directly influences whether development of a registry can proceed, and it can have a strong influence on how a registry is conducted. A regulatory agency looking for management of a therapeutic with a known toxicity profile may require a different registry design than a manufacturer with general questions about how a product is being used.

Typically, there are primary and secondary stakeholders for any registry. A primary stakeholder is usually responsible for creating and funding the registry. The party that requires the data, such as a regulatory authority, may also be considered a primary stakeholder. A secondary stakeholder is a party that would benefit from knowledge of the data or that would be impacted by the results but is not critical to establishing the registry. Treating clinicians and their patients could be considered secondary stakeholders. A partial list of possible stakeholders, both primary and secondary, follows:

- Public health or regulatory authorities.
- Product manufacturers.
- Health care service providers.
- Payer or commissioning authorities.
- Patients and/or advocacy groups.
- Treating clinician groups.
- Academic institutions or consortia.
- Professional societies.

Although interactions with potential stakeholders will vary, the registry will be best supported by defined interactions and communications with these parties. Defining these interactions during the planning stage will ensure that adequate dialog occurs and appropriate input is received to support the overall value of the registry. Interactions throughout the entire duration of the registry can also assure stakeholders that the registry is aligned with the purposes and goals that were set out during the planning stages and that the registry complies with all required guidances, rules, and/or regulations.

2.4. Assess Feasibility

A key element in determining the feasibility of developing a new registry relates to funding. Registries that meet the attributes described in this user's guide will most likely require significant funding. The degree of expense incurred will be determined by the scope of the registry, the rigor of data collection, and any audits that may be required. The larger the number of sites, number of patients, and scope of data collected, and the greater the need for representation of a wide variety of patient characteristics, the greater the expense will be. In addition, the method of data collection will contribute to expense. Historically, electronic data collection has been more expensive to implement, but generally less expensive to maintain, than forms that are faxed and scanned or mailed;[15] however, the cost difference for startup has been lessening. Funding will be affected by whether other relevant data sources and/or infrastructures exist that capture some of the information of interest; whether the registry adapts to new issues over time; and whether multiple funding sources participate. Funding needs should also be examined in terms of the projected life of the registry and/or its long-term sustainability.

There are many potential funding sources for registries. Funding sources are likely to want to share in planning and to provide input for the many choices that need to be made in the implementation plans. Funding sources may negotiate to receive access to deidentified data as a condition for their participation. Funding models for registries may vary significantly, and there is no preferred approach. Rather, the funding model for a registry should be dictated by the needs of the registry. Potential sources of funding include:

Foundations: Nonprofit disease foundations may be interested in a registry to track the natural history of the disease of interest as well as the impact of therapeutic interventions. Registries may be used to track practice patterns and outcomes for quality improvement initiatives. Ongoing registries can sometimes serve the additional purpose of assisting in recruitment for clinical trials.[16]

Government: Federal agencies, such as the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), the Agency for Healthcare Research and Quality (AHRQ), the Food and Drug Administration (FDA), and State agencies, may be interested in a registry to determine long-term outcomes of agents, devices, groups of drugs, or procedures. While the pharmaceutical industry or device manufacturers collect most long-term data on drug and device safety, many research questions arise that could potentially be suitable for government funding, ranging from clinical or comparative effectiveness to natural history of disease to the performance of health care providers based on accepted measures of quality of care. To determine if an agency might be interested in funding a registry, look for Requests for Proposals (RFPs) on its Web site. An RFP posting or direct communication with the appropriate agency staff may provide a great deal of specific information as to how a submission will be judged and what criteria would be needed in order for a proposal to be favorably ranked. Even if an RFP is not posted, contacting the appropriate agency staff may uncover potential interest in a registry to fill an unmet need.

Health plan providers: Under certain circumstances, health plan providers may be interested in funding a registry, since practical clinical research is increasingly viewed as a useful tool for providing evidence for health coverage and health care decisions.[17]

Patient groups: Patients may be able to contribute funding to focus on rare diseases or patient subgroups of interest for more common conditions. They may also contribute value in-kind.

Private funding: Private philanthropic individuals or charitable foundations and trusts may have an interest in furthering research to better understand the effects of a particular intervention or sets of interventions on a disease process.

Product manufacturers: Product manufacturers may be interested in studying the natural history of the disease for which they have (or are developing) a product; demonstrating the effectiveness and/or safety of existing products in real-world use through Risk Evaluation and Mitigation Strategy (REMS) programs as part of postmarketing commitments or requirements, or through studies; or assisting providers in evaluating or improving quality of care.

Professional societies: Health care professional associations are increasingly participating in developing or partnering with registries for scientific and quality measurement or improvement purposes.

Professional society/pharmaceutical industry "hybrids": Situations may exist in which a product manufacturer funds a registry designed and implemented by a professional society to gain insight into a set of research questions.

Multiple sponsors: Registries may meet the goals of multiple stakeholders, and such stakeholders may have an interest in sharing the funding. Registries for isotretinoin and antiretrovirals in pregnancy are examples, as is INTERMACS.[18] While multiple sponsorship can decrease the costs for each funding source, their varied interests and needs almost always increase the complexity and overall cost of the registry.

A public-private partnership is a service or business venture that is funded and operated through a partnership (contractual agreement) between a public agency (Federal, State, or local) and a private-sector entity or entities.[19] While some true public-private partnerships for registries currently exist (e.g., State-level immunization registries, bioterrorism surveillance),[20] [21] [22]there is great potential for growth in this approach. Both government and private sources have shown increasing interest in registries for improved safety monitoring, for comparative effectiveness goals, and for streamlining the costs of the drug development process.[23] [24] [25] [26] [27] [28] Several legislative actions have stated or suggested the role of public-private partnerships for activities such as registry development.[29] There are many good reasons for multiple stakeholders, including government agencies, providers, and industry, to work together for certain purposes. Thus, it is anticipated that shared funding mechanisms are likely to become more common. Chapter 24 provides more detail on the use of public-private partnerships to support registries.

2.5. Build a Registry Team

Several different kinds of knowledge, expertise, and skills are needed to plan and implement a registry. In a small registry run by a single individual, consultants may be able to provide the critical levels of expertise needed to plan all components of the registry. In a large registry, a variety of individuals may work together as a team to contribute the necessary expertise. Depending on the size, scope, and purpose of the registry, few, some, or all of the individuals representing the components of expertise described below may be included at the time of the planning process. Whatever number of individuals is eventually assembled, it is important to build a group that can work together as a collegial team to accomplish the goals of the registry. Additionally, the team participants must understand the data sources. By understanding the goals and data sources, the registry team will enable the data to be utilized in the most appropriate context for the most appropriate interpretation. The different kinds of expertise and experience that are useful include the following:

- *Project management*: Project management will be needed to coordinate the components of the registry; to manage timelines, milestones, deliverables, and budgets; and to ensure communication with sites, stakeholders, oversight committees, and funding sources. Ongoing oversight of the entire process will require a team approach. (See Establish a Governance and Oversight Plan.)
- *Subject matter*: A registry must be designed so that it contains the appropriate data to meet its goals as well as the needs of its stakeholders. For example, experts in the treatment of the clinical disease to be studied who are also familiar with the potential toxicities of the treatment(s) to be studied are critical to the success of the registry. Clinical experts must be able to apply all of the latest published clinical, toxicity, and outcome data to components of the registry and determine which elements are necessary, desirable, or superfluous. Depending on the outcomes and registry purpose, it is often useful to have patient representatives or advocates.

- *Registry science*: Epidemiology and biostatistics expertise specific to the subtleties of patient registries and observational research are very important in the design, implementation, and analysis of registry data. Epidemiologists can provide the study design and can work in collaboration with biostatisticians to develop a mutual understanding of the research objectives and data needed. Health outcomes researchers and economics researchers can also lend valuable expertise to the registry team. These scientists should work with the subject matter experts to ensure that appropriate analytic methods are being used to address the clinical issues relevant to achieving the goals of the registry.
- *Data collection and database management*: The decision to include various data elements can be made in consultation with experts in this field to place "critical fields" in a prominent and logical position on the data form for both paper-based and electronic data collection tools. (A final determination of what is usable and workable for data collection tools should be approved by all members of the team.) These experts may also need to write specific programs so that the data received from the registry are grouped, stored, and identified. They may generate reports for individuals who track registry participation, and they may provide data downloads periodically to registry analysts. This team will also be responsible for implementing and maintaining firewalls to protect the data according to accepted levels of security for similar collections of sensitive data.
- *Legal/patient privacy*: In the present legal climate, it is critical that either information that identifies individual patients be excluded or specific consent be sought to include information on the identity of a patient. The complexities of this topic are dealt with in detail in Chapters 7, 8, and 9. Legal and privacy expertise is needed to protect the patients and the owners of the database by ensuring that the registry complies with all national and local laws applicable to patient information.
- *Quality assurance*: As discussed in Chapter 11.3, quality assurance of procedures and data is another important component of registry success. Expertise in quality assurance will help in planning a good registry. The goals for quality assurance should be established for each registry, and the efforts made and the results achieved should be described.

2.6. Establish a Governance and Oversight Plan

Governance refers to guidance and high-level decisionmaking, including purpose, funding, execution, and dissemination of information. A goal of proper governance and oversight should be transparency to stakeholders in operations, decisionmaking, and reporting of results.

The composition and relative mix of stakeholders and experts relate largely to the purpose of the registry. For example, if the purpose of the registry is to determine a comparative effectiveness or reimbursement policy, those impacted by the policy should not solely govern the registry. Broad stakeholder involvement is most desirable in governance boards when there are many stakeholders. Depending on the size of the registry, governance may be assumed by various oversight committees made up of interested individuals who are part of the design team (internal governance) or who remain external to the day-to-day operations of the registry (external governance). Differences in the nature of the study questions, the overall resources being consumed by the registry, the soundness of the underlying data sources, and many other factors will influence the degree of involvement and role of oversight groups. In other words, the purpose of the committee functions described below is to lay out the roles that need to be assumed by the governance structure of many registries, but these should be individualized for a particular registry. It is also possible, if methods are clear and transparent, that oversight requirements may be minimal.

Registries fulfill governance roles in a variety of ways. Many of the roles, for example, could be assumed by a single committee (e.g., a steering committee) in some registries. Whatever model is adopted, it must

accommodate all of the working constituencies and provide a mechanism for these individuals to work together to achieve the goals of the registry.

All aspects of governance should be codified in a written format that can be reviewed, shared, and refined over time. In addition, governance is a dynamic process, subject to change in policy as evidence emerges that is likely to lead to improvements in the process.

Governance and oversight functions that may be considered include:

- *Executive or steering*: This function assumes responsibility for the major financial, administrative, legal/ethical, and scientific decisions that determine the direction of the registry. These decisions are made with appropriate input from legal, scientific, and administrative experts. Depending on their capabilities and the size and resources of the registry, the group serving the steering function may also assume some of the functions described below.
- *Scientific*: This function may include experts in areas ranging from database content, to general clinical research, to epidemiology and biostatistics. This function may determine the overall direction of database inquiries and recommend specific analyses to the executive or steering group. It is strongly desirable that the reports that emerge from a registry be scientifically based analyses that are independent and transparent.[30] To enhance credibility and in the interest of full disclosure, the role of all stakeholders in the publication process should be specified and any potential conflicts of interest identified.
- *Liaison*: In large registries, a function may be specified to focus on maintaining relationships with the funding source, health care providers, and patients who need access to registry information. The group serving this function may develop monitoring and satisfaction tools to assure that the day-today operations of the registry remain healthy.
- *Adjudication*: Adjudication is used to review and confirm cases (outcomes) that may be difficult to classify. Individuals performing this function are generally blinded to the exposure (product or process) under study so that the confirmation of outcomes is made without knowledge of exposure.
- *External review*: External review committees and/or advisory boards can be useful for providing independent oversight throughout the course of the registry. The majority of registries will not require a data safety monitoring board (DSMB), since a DSMB is commonly used in situations where data are randomized and treatment status is blinded. However, there may be situations in which the registry is responsible for the primary accumulation of safety data on a particular intervention; in such situations, an external committee or DSMB would be useful for conducting periodic reviews (e.g., annually).
- *Data access, use, and publications*: This function should address the process by which registry investigators access and perform analyses of registry data for the purpose of submitting abstracts to scientific meetings and developing manuscripts for peer-reviewed journal submission. Authorship (including that of registry sponsors) in scientific publications should satisfy the conditions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[31] The rules governing authorship may be affected by the funding source, as in the case of NIH or foundation funding, or by the biomedical journal. (See Case Examples 1 and 19.) Other investigators may request permission to access the data. For example, a Ph.D. candidate at an institution might seek registry-wide aggregate data for the purpose of evaluating a new scientific question. A process for reviewing and responding to such requests from other investigators or entities should be considered in some registries that may generate broad external interest if the registry stakeholders and participants are agreeable to such use.

2.7. Consider the Scope and Rigor Needed

2.7.1. Scope of Data

The scope of a registry may be viewed in terms of size, setting, duration, geography, and financing. The purpose and objectives of the registry should frame the scope, but other factors (aside from feasibility) may ultimately shape it. For example, the scope may be affected by:

- Regulatory requirements, such as those imposed by the FDA as a condition of product marketing.
- Reimbursement decisions, such as national coverage decisions by CMS or "Prior Authorization" requirements used by health insurers in some situations.
- National research interests, such as those driven by NIH.
- Public health policy, such as CDC policy and immunization policy.

The scope is also affected by the degree of uncertainty that is acceptable to the primary stakeholders, with that uncertainty being principally driven by the quantity, quality, and detail of the data collection balanced against its considered importance and value. Therefore, it is critical to understand the potential questions that may or may not be answerable because of the quantity and quality of the data. It should also be noted that the broader the audience of stakeholders is, the broader the list of questions will be that may need to be included. This increased breadth can result in an increase in the number of patients who need to be enrolled and/or data points that need to be collected in order to meet the objective of the registry with an acceptable level of precision.

Some of the specific variables that can characterize the scope of a registry include:

- *Size*: This refers to the number and complexity of data points, the frequency of data collection and to the enrollment of investigators and patients. A registry with a large number of complex data points may allow for detailed and thoughtful analyses but may be so burdensome as to discourage investigator and patient enrollments. In turn, a small registry with few patients and data points may be easier to execute, but the data could lack depth and be less meaningful.[32] Size also determines the precision with which measures of risk or risk difference can be calculated.
- *Duration*: The planning of a registry must reflect the length of time that the registry is expected to collect the data in order to achieve its purpose and provide analysis of the data collected. Some registries are limited by commercial interests, such as when the product under study is approach the end of its patent life.
- *Setting*: This refers to the specific setting through which the registry will recruit investigators and patients as well as collect data (e.g., hospital, doctor's office, pharmacy, home).
- *Geography*: The setup, management, and analysis of a locally run registry represent a very different scope than the setup, management, and analysis of a global registry. A global registry poses challenges (e.g., language, cultural, time zone, regulatory) that must be taken into consideration in the planning process.
- *Cost*: The scope of a registry will determine the cost of creating, managing, and analyzing the registry. Budgetary constraints must be carefully considered before moving from conception to reality. Additionally, the value of the information is a factor in the financial decisions. Certain choices in planning, such as building on existing infrastructure and/or linking to data sources relevant to the purposes of the registry, may increase the net return.
- *Richness of clinical data needed*: In some situations, the outcome may be relatively simple to characterize (e.g., death). In other cases, the focus of interest may be a complex set of symptoms and measurements (e.g., for Churg-Strauss Syndrome) or may require specialized diagnostic testing or tissue sampling (e.g., sentinel node in melanoma). Some outcomes may require

assessment by an independent third party. Depending on the objectives of the registry, collection and storage of biological samples may be considered. (See Section 2.7.3 below.) The collection of biosamples itself is a rapidly evolving field, and registry developers should consult both technical and legal sources regarding how to include biosamples in a registry.

2.7.2. When Data Need To Be Available for Analysis

Meaningful data on disease progression or other long-term patient outcomes may not be available through a registry for many years, whereas safety data could be examined periodically over time. Therefore, the type of data on patient outcomes and when they will be available for analysis should be addressed from the perspective of the intended uses of the data in both the short term and long term. For industry-sponsored registries, if planning begins at an early stage, it may be possible to consider whether to align registry questions with those from the clinical trial (where appropriate) so that some data can carry over for more comprehensive longitudinal analyses.

2.7.3. Scientific Rigor

The content of the data to be collected should be driven by the scientific analyses that are planned for the registry, which, in turn, are determined by the specific objectives of the registry. A registry that is designed primarily for monitoring safety will inevitably contain different data elements from one that is designed primarily for monitoring effectiveness. Similarly, the extent to which data need to be validated will depend on the purpose of the registry and the complexity of the clinical information being sought. For some outcomes, clinical diagnosis may be sufficient; for others, supporting documents from hospitalizations, referrals, or biopsies may be needed; and for others, formal adjudication by a committee may be required. Generally, registries that are undertaken for regulatory decisionmaking will require increased attention toward diagnostic confirmation (i.e., enhanced scientific rigor).

2.8. Define the Core Dataset, Patient Outcomes, and Target Population

2.8.1. Core Dataset

Elements of data to be included must have potential value in the context of the current scientific and clinical climate and must be chosen by a team of experts, preferably with input from experts in biostatistics and epidemiology. Each data element should relate to the purpose and specific objectives of the registry. Ideally, each data element should address the central questions for which the registry was designed. It is useful to consider the generalizability of the information collected, as appropriate. For example, when seeking information on cost-effectiveness, it may be preferable to collect data on resource utilization rather than actual costs of this utilization, since the broader descriptor can be more easily generalized to other settings and cost structures. While a certain number of "speculative" fields may be desired to generate and explore hypotheses, these must be balanced against the risk of overburdening sites with capturing superfluous data. A plan for quality assurance should be considered in tandem with developing the core dataset.

The core dataset variables ("need to know") define the information set needed to address the critical questions for which the registry was created. At a minimum, when calculating the resource needs and overall design of the registry, registry planners must account for these fields. If additional noncore variables ("nice to know") are included, such as more descriptive or exploratory variables, it is important that such data elements align with the goals of the registry and take into account the burden of data

collection and entry at the site level. A parsimonious use of "nice to know" variables is important for several reasons.

First, when data elements change, there is a cascade effect to all dependent components of the registry process and outputs. For example, the addition of new data elements may require changes to the data collection system, retraining of site personnel on data definitions and collection practices, adjustments to the registry protocol, and amendment submissions to institutional review boards. Such changes often require additional financial resources. Ideally, the registry would both limit the total number of data elements and include, at the outset, data elements that might change from "nice to know" to "need to know" during the course of the registry. In practice, this is a difficult balance to achieve, so most registries should plan adequate resources to be used for change management.

Second, a registry should avoid attempting to accomplish too many goals, or its burden will outweigh its usefulness to the clinical sites and researchers. Examples exist, however, of registries that serve multiple purposes successfully without overburdening clinicians. (See Case Example 1.)

Third, even "need-to-know" variables can sometimes be difficult to collect reliably (e.g., use of illegal substances) or without substantial burden (e.g., unusual laboratory tests). Even with a limited core dataset, feasibility must still be considered. (See Chapter 4)

Fourth, it is useful to consider what data are already available and/or collected and what additional data need to be collected. When determining additional data elements, it is imperative to consider whether the information desired is consistent with general practice or whether it might be more intensive or exceeding usual practice. For some purposes, collecting specific laboratories or additional visits may be necessary, but could change how the registry is perceived by institutional review boards or ethics committees. The distinction between "interventional" and "observational" is straightforward in terms of random assignment to treatment, but some registries with requirements that exceed a threshold of usual practice in Europe, for example, may be subject to additional requirements more typical of "interventional" research. In Chapter 1.7.1 of Volume 9A of the Rules Governing Medicinal Products in the European Union,[33] it has been clarified that registries may "collect a battery of information using standardized questionnaires in a prospective fashion" and "questionnaires, by themselves, are not considered interventional." These rules also state that

- "[T]he assignment of a patient to a particular strategy is not decided in advance by a [trial] protocol but falls within the current practice…"
- "[N]o additional diagnostic or monitoring procedures shall be applied to patients."

This last requirement can be challenging to interpret since registries sometimes perform diagnostic tests that are consistent with general practice but may be performed more frequently than would be the case in general practice. The determination that a registry should be considered "interventional" from a regulatory perspective can add significant burden and cost to the registry program, and, as such, the tradeoffs must be carefully considered in planning registry visits and data or specimen collection.

Finally, it is important to consider patient privacy, national and international rules concerning ethics, and regulatory requirements to assure that the registry data requirements do not jeopardize patient privacy or put institutional/ethics reviews and approvals at risk.

2.8.2. Patient Outcomes

The outcomes of greatest importance should be identified early in the concept phase of the registry. Delineating these outcomes (e.g., primary or secondary endpoints) will force registry designers to establish priorities. Prioritization of interests in the planning phase will help focus the work of the registry and will guide study size requirements. (See Chapter 3.) Identifying the patient outcomes of the greatest importance will also help to guide the selection of the dataset. Avoiding the temptation to collect "nice to know" data that are likely of marginal value is of paramount importance, yet some registries do, in fact, need to collect large amounts of data to accomplish their purposes. Possessing adequate data in order to properly address potential confounders during analyses is one reason that extensive data collection is sometimes required.[34]

Methods to ascertain the principal outcomes should be clearly established. The diagnostic requirements, level of data detail, and level of data validation and/or adjudication should also be addressed. As noted below in the context of identifying a target population, relying on established guidelines and standards to aid in defining outcomes of interest has many benefits and should be considered.

The issues of ascertainment noted here are important to consider because they will have a bearing on some attributes by which registries may be evaluated.[35] These attributes include sensitivity (the extent to which the methods identify all outcomes of interest) and external validity (generalizability to similar populations), among others.

2.8.3. Target Population

The target population is the population to which the findings of the registry are meant to apply. It must be defined for two basic reasons. First, the target population serves as the foundation for planning the registry. Second, it also represents a major constituency that will be impacted by the results of the registry.

One of the goals for registry data may be to enable generalization of conclusions from clinical research on narrowly defined populations to broader ones, and therefore the inclusion criteria for most (although not all) registries are relatively broad. As an example, screening criteria for a registry may allow inclusion of elderly patients, patients with multiple comorbidities, patients on multiple therapies, patients who switch treatments during the period of observation, or patients who are using products "off label." The definition of the target population will depend on many factors (e.g., scope and cost), but ultimately will be driven by the purpose of the registry.

As with defining patient outcomes, target population criteria and/or definitions should be consistent with established guidelines and standards within the therapeutic area. Achieving this goal increases the potential utility of the registry by leveraging other data sources (historical or concurrent) with different information on the same target population and enhancing statistical power if similar information is collected on the target population.

In establishing target population criteria, consideration should be given to the feasibility of access to that population. One should try to distinguish the ideal from the real. Some questions to consider in this regard are:

- How common is the exposure or disease of interest?

- Can eligible persons be readily identified?
- Are other sources competing for data on the same patients?
- Is care centralized or dispersed (e.g., in a referral or tertiary care facility)?
- How mobile is the target population?

Ultimately, methods to ascertain members of the target population should be carefully considered (e.g., use of screening logs that identify all potential patients and indicate whether they participate and, if not, why not), as should the use of sources outside the registry (e.g., patient groups). Greater accessibility to the target population will reap benefits in terms of enhanced representativeness and statistical power.

Lastly, thought should be given to comparison (control) groups either internal or external to the registry. Again, much of this consideration will be driven by the purpose and specific objectives of the registry. For example, natural history registries do not need controls, but controls are especially desirable for registries created to evaluate comparative effectiveness or safety.

2.9. Develop a Study Plan or Protocol

The study plan documents the objectives of the registry and describes how those objectives will be achieved. At a minimum, the study plan should include the registry objectives, the eligibility criteria for participants, and the data collection procedures. Ideally, a full study protocol will be developed to document the objectives, design, participant inclusion/exclusion criteria, outcomes of interest, data to be collected, data collection procedures, governance procedures, and plans for complying with ethical obligations and protecting patient privacy.

In addition to a study plan or protocol, registries may have statistical analysis plans. Chapters 13 and 25 discuss the importance of analysis plans.

2.10. Develop a Project Plan

Developing an overall project plan is critically important so that the registry team has a roadmap to guide their collective efforts. Depending on the complexity of the registry project, the project plan may include some or all of the following elements:

- Scope management plan to control the scope of the project. It should provide the approach to making changes to the scope through a clearly defined change-control system.
- Detailed timeline and schedule management plan to ensure that the project and its deliverables are completed on time.
- Cost management plan for keeping project costs within the budget. The cost management plan may provide estimates on cost of labor, purchases and acquisitions, compliance with regulatory requirements, etc. This plan should be aligned with the change-control system so that all changes to the scope will be reflected in the cost component of the registry project.
- Quality management plan to describe the procedures to be used to test project concepts, ideas, and decisions in the process of building a registry. Having a quality management plan in place can help in detecting design errors early, formulating necessary changes to the scope, and ensuring that the final product meets stakeholders' expectations.
- Staffing management plan to determine what skills will be needed and when to meet the project goals. (See Chapter 2.2.5).
- Communication plan that includes who is responsible for communicating information and to whom it should be communicated. Considerations include different categories of information,

frequency of communications, and methods of communication. It also should provide steps to escalate issues that cannot be resolved on a lower staff level.

- Procurement plan for external components or equipment and/or outsourced software development for the planned registry, if pertinent. Such a plan should describe how the procurement process would be managed within the organization. Decisions to procure products or services may have a direct impact on other components of the project plan, including the staffing plan and timeline.
- Risk management plan to identify and mitigate risks. Many project risks are predictable events, and therefore they can and should be assessed in the very early stages of registry planning. It is important to prioritize project risks by their potential impact on the specific objectives and to develop an adequate risk response plan for the most significant risks. Some predictable risks include:
    - Disagreement between stakeholders over the scope of specific tasks.
    - Inaccurate cost estimates.
    - Delays in the timeline.

3. Summary

In summary, planning a patient registry involves several key steps, including articulating its purpose, determining whether it is an appropriate means of addressing the research question, identifying stakeholders, defining the scope and target population, assessing feasibility, and securing funding. A registry team and advisors must be assembled to develop, coordinate, and guide the registry; these individuals should be selected based on their expertise and experience. Governance and oversight for the registry should also be addressed during the planning phase. While registries differ tremendously in size, scope, and resource requirements, the basic elements of planning described here are relevant for most, if not all registries, and can help to support the launch and operation of a successful registry.

References for Chapter 2

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Case Examples for Chapter 2

Case Example 1. Creating a Registry to Fulfill Multiple Purposes and Using a Publications Committee to Review Data Requests

Description	The National Registry of Myocardial Infarction (NRMI) collected, analyzed, and disseminated data on patients experiencing acute myocardial infarction. Its goal was improvement of patient care at individual hospitals through the hospital team's evaluation of data and assessment of care delivery systems.
Sponsor	Genentech, Inc.
Year Started	1990
Year Ended	2006
No. of Sites	451 hospitals (NRMI 5). Over 2,150 hospitals participated in NRMI over 16 years.
No. of Patients	2,515,106

Challenge

Over the past 20 years, there have been significant changes in the treatment of acute myocardial infarction (AMI) patients. Evidence from large clinical trials has led to the introduction of new guidelines and therapies for treating AMI patients, including fibrinolytic therapy and percutaneous coronary intervention. While these treatments can improve both morbidity and mortality for AMI patients, they are time sensitive and must be administered very soon after hospital arrival in order to be most effective.

After the release of its first fibrinolytic therapy product in 1987, the sponsor's field representatives learned from their discussions with emergency department physicians, cardiologists, and hospital staff that most clinicians believed they were treating patients quickly, although there was no documentation or benchmarking to confirm this assumption or to identify and correct delays. At that time, many emergency departments did not have readily available diagnostic tools (such as angiography labs), and hospitals with AMI-specific decision pathways and treatment protocols were the exception rather than the rule.

In addition, since fibrinolytic therapy was being widely used for the first time, the sponsor wanted to gather safety information related to its use in real-world situations and in a broader range of patients than those treated in the controlled environment of a clinical trial.

Proposed Solution

The sponsor decided to create the registry to fulfill the multiple purposes of identifying treatment patterns, promoting time-to-treatment and other quality improvements, and gathering real-world safety data. The scope of the data collection necessary to meet these needs could have made such a registry impracticable, so the project team faced the sizable challenge of balancing the data needs with the feasibility of the registry.

The sponsor formed a scientific advisory board with members representing the various clinical stakeholders (emergency department, cardiology, nursing, research, etc.). The scientific advisory board developed the dataset for the registry, keeping a few guiding principles in mind. These principles emphasized maintaining balance between the clinical research and the feasibility of the registry. The first principle was to determine whether the proposed data element was necessary by asking several key questions: How will the data element be used in generating hospital feedback reports or research analyses? Is the data element already collected? If not, should it be collected? If it should be collected, is it feasible to collect those data? The second principle focused on using existing data standards whenever possible. If a data standard did not exist, the team tried to collect the data in the simplest possible way. The third principle emphasized data consistency and making the registry user friendly by continually refining data element definitions until they were as clear as possible.

In 1990, the sponsor launched the registry. During the 16 years that the registry was conducted, it demonstrated that the advisory board's efforts to create a feasible multipurpose registry were successful. The registry collected data on the clinical presentation, treatment, and outcomes of over 2.5 million patients with AMI from more than 2,150 participating sites.

The success of the registry presented a new challenge for the registry team. The sponsor received a large volume of requests to analyze the registry data, often for research topics that fell outside of the standardized reports developed for the registry. As a guiding principle, the registry team was committed to making the data available for research projects, but it had limited resources. To support these requests, the team developed a process that would allow outside researchers to access the registry data without overburdening the registry team.

The registry team created a publication process to determine when another group could use the data for research. The team set high-level criteria for all data requests: the analysis had to be feasible given the data in the registry, and the request could not represent a duplication of another research effort.

The registry team involved its scientific advisory board, made up of cardiologists, emergency department physicians, nurses, research scientists, pharmacists, and reviewers with specialties in biostatistics and statistical programming, in creating a publication review committee. The review committee evaluated all research proposals to determine originality, interest to peers, feasibility, appropriateness, and priority. The review committee limited its review of research proposals to a set number of reviews per year, and scheduled the reviews and deadlines around the abstract deadlines for the major cardiology conferences. Research analyses had to be intended to result in peer-reviewed presentations and publications. Researchers were asked to submit proposals that included well-defined questions and an analysis plan. If the proposal was accepted, the researchers discussed any further details with the biostatisticians and statistical programmers who performed the analyses (and who were employed at an independent clinical research organization). The results were sent directly to the researchers.

The scientific advisory board and review committee remained involved in the process after a data request had been granted. All authors submitted their abstracts to the review committee before sending

them to conferences. The review committee offered constructive criticism to help the authors improve their abstracts. The review committee also reviewed manuscripts before journal submission to help identify any issues or concerns that the authors should address.

Results

This publication process enabled the wealth of data collected in this registry to be used in over 150 scientific abstracts and 100 peer-reviewed articles, addressing each of the purposes of the registry as well as other research topics. By involving the scientific advisory board and providing independent biostatistical support, the registry team developed an infrastructure that enhanced the credibility of the research uses of this observational database.

Key Point

Registries can be developed to fulfill more than one purpose, but this added complexity requires careful planning to ensure that the final registry data collection burden and procedures are feasible. Making sure that the advisory board includes representatives with clinical and operational perspectives can help the board to maintain its focus on feasibility. As a registry database gains large amounts of data, the registry team will likely receive research proposals from groups interested in using the data. The registry team may want to set up a publication process during the registry design phase.

For More Information

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Chapter 3. Registry Design

1. Introduction

This chapter is intended as a high-level practical guide to the application of epidemiologic methods that are particularly useful in the design of registries that evaluate patient outcomes. Since it is not intended to replace a basic textbook on epidemiologic design, readers are encouraged to seek more information from textbooks and scientific articles. Table 1 summarizes the key considerations for study design that are discussed in this chapter. Throughout the design process, registry planners may want to discuss options and decisions with the registry stakeholders and relevant experts to ensure that sound decisions are made. The choice of groups to be consulted during the design phase generally depends on the nature of the registry, the registry funding source and funding mechanism, and the intended audience for registry reporting. More detailed discussions of registry design for specific types of registries are provided in Chapters 19, 20, 21, 22, and 23.

Table 1. Considerations for Study Design

Construct	Relevant questions
Research question	What are the clinical and/or public health questions of interest?
Resources	What resources, in terms of funding, sites, clinicians, and patients, are available for the study?
Exposures and Outcomes	How do the clinical questions of interest translate into measurable exposures and outcomes?
Data sources	Where can the necessary data elements be found?
Study design	What types of design can be used to answer the questions or fulfill the purpose?
Study population	What types of patients are needed for study? Is a comparison group needed? How should patients be selected for study?
Sampling	How should the study population be sampled, taking into account the target populations and study design?
Study size and duration	For how long should data be collected, and for how many patients?
Internal and external validity	What are the potential biases? What are the concerns about generalizability of the results (external validity)?

2. Research Questions Appropriate for Registries

The questions typically addressed in registries range from purely descriptive questions aimed at understanding the characteristics of people who develop the disease and how the disease generally progresses, to highly focused questions intended to support decisionmaking. Registries focused on determining clinical effectiveness or cost-effectiveness or assessing safety or harm are generally hypothesis driven and concentrate on evaluating the effects of specific treatments on patient outcomes. Research questions should address the registry's purposes, as broadly described in Table 2.

Observational studies derived from registries (or "registry-based studies") are an important part of the research armamentarium alongside interventional studies, such as randomized controlled trials (RCTs) or pragmatic trials, and retrospective studies, such as studies derived exclusively from administrative claims data. Each of these study designs has strengths and limitations, and the selection of a study design should

be guided by the research questions of interest. (See Section 2.2.2 for a discussion of the factors that influence the study design decision.) In some cases, multiple studies with different designs or a hybrid study that combines study designs will be necessary to address a research question. In fact, this more comprehensive approach to evidence development is likely to become more common as researchers strive to address multiple questions for multiple stakeholders most efficiently. Observational studies and interventional studies are more complementary than competitive, precisely because some research questions are better answered by one method than the other. Interventional studies are considered by many to provide the highest grade evidence for evaluating whether a drug has the ability to bring about an intended effect in optimal or "ideal world" situations, a concept also known as "efficacy."[1] Observational designs, on the other hand, are particularly well suited for studying broader populations, understanding actual results (e.g., some safety outcomes) in real world practice (see Case Example 2), and for obtaining more representative quality of life information. This is particularly true when the factors surrounding the decision to treat are an important aspect of understanding treatment effectiveness.[2]

Table 2. Overview of Registry Purposes

• Assessing natural history, including estimating the magnitude of a problem; determining the underlying incidence or prevalence rate of a condition; examining trends of disease over time; conducting surveillance; assessing service delivery and identifying groups at high risk; documenting the types of patients served by a health provider; and describing and estimating survival.
• Determining clinical effectiveness, cost-effectiveness, or comparative effectiveness of a test or treatment, including for the purpose of determining reimbursement.
• Measuring or monitoring safety and harm associated with the use of specific products and treatments, including conducting comparative evaluation of safety and effectiveness.
• Measuring or improving quality of care, including conducting programs to measure and/or improve the practice of medicine and/or public health.

In many situations, nonrandomized comparisons either are sufficient to address the research question or, in some cases, may be necessary because of the following issues with randomizing patients to a specific treatment:

- *Equipoise:* Can providers ethically introduce randomization between treatments when the treatments may not be clinically equivalent?
- *Ethics:* If reasonable suspicion about the safety of a product has become known, would it be ethical to conduct a trial that deliberately exposes patients to potential harm? For example, can pregnant women be ethically exposed to drugs that may be teratogenic? (See Chapter 21 and Case Examples 46, 47, 48, and 49.)
- *Practicality:* Will patients enroll in a study where they might not receive the treatment, or might not receive what is likely to be the best treatment? How can compliance and adherence to a treatment be studied, if not by observing what people do in real-world situations?

Registries are particularly suitable for some types of research questions, such as:

- Natural history studies where the goal is to observe clinical practice and patient experience but not to introduce any intervention.
- Measures of clinical effectiveness, especially as related to compliance, where the purpose is to learn about what patients and practitioners actually do and how their actions affect real-world outcomes. This is especially important for treatments that have poor compliance.

- Studies of effectiveness and safety for which clinician training and technique are part of the study of the treatment (e.g., a procedure such as placement of carotid stent).
- Studies of heterogeneous patient populations, since unlike randomized trials, registries generally have much broader inclusion criteria and fewer exclusion criteria. These characteristics lead to studies with greater generalizability (external validity) and may allow for assessment of subgroup differences in treatment effects.
- Followup for delayed or long-term benefits or harm, since registries can extend over much longer periods than most clinical trials (because of their generally lower costs to run and lesser burden on participants).
- Surveillance for rare events or of rare diseases.
- Studies for treatments in which randomization is unethical, such as intentional exposure to potential harm (as in safety studies of marketed products that are suspected of being harmful).
- Studies for treatments in which randomization is not necessary, such as when certain therapies are only available in certain places owing to high cost or other restrictions (e.g., proton beam therapy).
- Studies for which blinding is challenging or unethical (e.g., studies of surgical interventions, acupuncture).
- Studies of rapidly changing technology.
- Studies of conditions with complex treatment patterns and treatment combinations.
- Studies of health care access and barriers to care.
- Evaluations of actual standard medical practice. (See Case Example 55.)

Registry studies may also include embedded substudies as part of their overall design. These substudies can themselves have various designs (e.g., highly detailed prospective data collection on a subset of registry participants, or a case-control study focused on either incident or prevalent cases identified within the registry). (See Case Examples 3 and 44.) Registries can also be used as sampling frames for RCTs.

3. Translating Clinical Questions into Measurable Exposures and Outcomes

The specific clinical questions of interest in a registry will guide the definitions of study subjects, exposure, and outcome measures, as well as the study design, data collection, and analysis. In the context of registries, the term "exposure" is used broadly to include treatments and procedures, health care services, diseases, and conditions.

The clinical questions of interest can be defined by reviewing published clinical information, soliciting experts' opinions, and evaluating the expressed needs of the patients, health care providers, and payers. Examples of research questions, key outcome and exposure variables, and sources of data are shown in Table 3. As these examples show, the outcomes (generally beneficial or deleterious outcomes) are the main endpoints of interest posed in the research question. These typically represent measures of health or onset of illness or adverse events, but also commonly include quality of life measures, and measures of health care utilization and costs.

Relevant exposures also derive from the main research question and relate to why a patient might experience benefit or harm. Evaluation of an exposure includes collection of information that affects or augments the main exposure, such as dose, duration of exposure, route of exposure, or adherence. Other variables of interest include independent risk factors for the outcomes of interest (e.g., comorbidities, age), as well as variables known as potential confounding variables, that are related to both the exposure

and the outcome and are necessary for conducting valid statistical analyses. Confounding can result in inaccurate estimates of association between the study exposure and outcome through mixing of effects. For example, in a study of asthma medications, prior history of treatment resistance should be collected or else results may be biased. The bias could occur because treatment resistance may relate both to the likelihood of receiving the new drug (meaning that doctors will be more likely to try a new drug in patients who have failed other therapies) and the likelihood of having a poorer outcome (e.g., hospitalization). Refer to Chapter 4 for a discussion of selecting data elements and Chapter 5 for a discussion of selecting patient reported outcomes.

Table 3. Examples of Research Questions and Key Exposures and Outcomes

Research Question	Key exposure (source of data)	Key outcome (source of data)
What is the expected time to rejection for first kidney transplants among adults, and how does that differ according to immunosuppressive regimen?	All immunosuppressants, including dosage and duration (clinician or medical record)	Organ rejection (clinician or medical record)
Are patients using a particular treatment better able to perform activities of daily living than others?	Treatments for disease of interest (clinician or medical record)	Ability to independently perform key activities related to daily living (patient)
Do patients undergoing gastric bypass surgery for weight loss utilize fewer health care resources in the year following surgery?	Surgery (clinician or medical record)	Number of inpatient and outpatient visits, medications dispensed, associated costs (administrative databases, clinician, or medical record)
Are patients using a particular drug more likely to have serious adverse pregnancy outcomes?	Drug use by mother during pregnancy (clinician, medical record, or patient)	Pregnancy outcome (clinician, medical record, or patient)

4. Finding the Necessary Data

The identification of key outcome and exposure variables and patients will drive the strategy for data collection, including the choice of data sources. A key challenge to registries is that it is generally not possible to collect all desired data. As discussed in Chapter 4, data collection should be both parsimonious and broadly applicable. For example, while experimental imaging studies may provide interesting data, if the imaging technology is not widely available, the data will not be available for enough patients to be useful for analysis. Moreover, the registry findings will not be generalizable if only sophisticated centers that have such technology participate. Instead, registries should focus on collecting relevant data with relatively modest burden on patients and clinicians. Registry data can be obtained from patients, clinicians, medical records, and linkage with other sources (in particular, extant databases), depending on the available budget. (See Chapters 6, 15, and 16.)

Examples of patient-reported data include health-related quality of life; utilities (i.e., patient preferences); symptoms; use of over-the-counter (OTC), complementary, and alternative medication; behavioral data (e.g., smoking and alcohol use); family history; and biological specimens. These data may rely on the subjective interpretation and reporting of the patient (e.g., health-related quality of life, utilities, symptoms such as pain or fatigue); may be difficult to otherwise track (e.g., use of complementary and alternative medication, smoking, and alcohol use); or may be unique to the patient (e.g., biological

specimens). Health care resource utilization is another important construct that reflects both cost of care (burden of illness) and health-related quality of life. For example, more frequent office visits, procedures, or hospitalizations may result in reduced health-related quality of life for the patient. The primary advantage of this form of data collection is that it provides direct information from the entity that is ultimately of the most interest—the patient. The primary disadvantages are that the patient is not necessarily a trained observer and that various forms of bias, such as recall bias, may influence subjective information. For example, people may selectively recall certain exposures because they believe they have a disease that was caused by that exposure, or their recall may be influenced by recent news stories claiming cause-and-effect relationships. (See Case Example 4.)

Examples of clinician data include clinical impressions, clinical diagnoses, clinical signs, differential diagnoses, laboratory results, and staging. The primary advantage of clinician data is that clinicians are trained observers. Even so, the primary disadvantages are that clinicians are not necessarily accurate reporters of patient perceptions, and their responses may also be subject to recall bias. Moreover, the time that busy clinicians can devote to registry data collection is often limited.

Medical records also are a repository of clinician-derived data. Certain data about treatments, risk factors, and effect modifiers are often not consistently captured in medical records of any type, but where available, can be useful. Examples of such data that are difficult to find elsewhere include OTC medications, smoking and alcohol use, complementary and alternative medicines, and counseling activities by the clinician on lifestyle modifications. Medical records are often relied upon as a source of detailed clinical information for adjudication by external reviewers of medical diagnoses corresponding to study endpoints.

Electronic medical records, increasingly available, improve access to the data within medical records. The increasing use of electronic health records has facilitated the development of a number of registries within large health plans. Kaiser Permanente has created several registries of patients receiving total joint replacement, bariatric surgery, and nonsurgical conditions (e.g., diabetes), all of which rely heavily on existing electronic health record data. As discussed further in Chapter 15, the availability of medical records data in electronic format does not, by itself, guarantee consistency of terminology and coding.

Examples of other data sources include health insurance claims, pharmacy data, laboratory data, other registries, and national datasets, such as Medicare claims data and the National Death Index. These sources can be used to supplement registries with data that may otherwise be difficult to obtain, subject to recall bias, not collected because of loss to followup, or likely inaccurate by self-report (e.g., in those patients with diseases affecting recall, cognition, or mental status). See Table 9 in Chapter 6 for more information on data sources.

5. Resources and Efficiency

Ideally, a study is designed to optimally answer a research question of interest and funded adequately to achieve the objectives based on the requirements of the design. Frequently, however, finite resources are available at the outset of a project that constrain the approaches that may be pursued. Often, through efficiencies in the selection of a study design and patient population (observational vs. RCT, case-control vs. prospective cohort), selection of data sources (e.g., medical-records-based studies vs. information collected directly from clinicians or patients), restriction of the number of study sites, or other approaches,

studies may be planned that provide adequate evidence for addressing a research question, in spite of limited resources.

Section 6 below discusses how certain designs may be more efficient for addressing some research questions.

6. Study Designs for Registries

Although studies derived from registries are, by definition, observational studies, the framework for how the data will be analyzed drives the data collection and choices of patients for inclusion in the study.

The study models of case series, cohort, case-control, and case-cohort are commonly applied to registry data and are described briefly here. When case-control or case-cohort designs are applied to registry data, additional data may be collected to facilitate examination of questions that arise. Before adding new data elements, whether in a nested substudy or for a new objective, the steps outlined in Chapter 2 (e.g., assess feasibility, determine scope, evaluate regulatory/ethical impact) should be undertaken. Other models that are also useful in some situations, but are not covered here, include: case-crossover studies, which are efficient designs for studying the effects of intermittent exposures (e.g., use of erectile dysfunction drugs) on conditions with sudden onset, and quasi-experimental studies or "pragmatic trials." For example, in a pragmatic trial, providers may be randomized as to which intervention or quality improvement tools they use, but patients are observed without further intervention. Also, there has been recent interest in applying the concept of adaptive clinical trial design to registries. An adaptive design has been defined as a design that allows adaptations or modifications to some aspects of a clinical trial after its initiation without undermining the validity and integrity of the trial.[3] While many long-term registries are modified after initiation, the more formal aspects of adaptive trial design have yet to be applied to registries and observational studies.

Determining what framework will be used to analyze the data is important in designing the registry and the registry data collection procedures. Readers are encouraged to consult textbooks of epidemiology and pharmacoepidemiology for more information. Many of the references in Chapters 13 and 18 relate to study design and analysis.

6.1. Case Series

Using a registry population to develop case series is a straightforward application that does not require sophisticated analytics. Depending on the generalizability of the registry itself, case series drawn from the registry can be used to describe the characteristics to be used in comparison to other case series (e.g., from spontaneous adverse event reports). Self-controlled methods, including self-controlled case series are a relatively new set of methods that lends itself well to registry analyses as it focuses on only those subjects who have experienced the event of interest and uses an internal comparison to derive the relative (not absolute) incidence of the event during the time the subject is 'exposed' compared to the incidence during time where they are 'unexposed'.[4] This design implicitly controls for all confounders that do not vary over the follow-up time (e.g., gender, genetics, geographic area) as the subject serves as their own control. It also may be very useful in those circumstances where a comparison group is not available. Self-controlled case series require that the probability of exposure is not affected by the occurrence of an outcome and, for non-recurrent events, the method works only when the event risk is small and varies over the follow-up time. Derivative methods, grouped as self-controlled cohort methods, include

observational screening[5] and temporal pattern discovery,[6] and compare the rate of events post-exposure with the rate of events pre-exposure among patients with at least one exposure.

6.2. Cohort

Cohort studies follow, over time, a group of people who possess a characteristic, to see if they develop a particular endpoint or outcome. Cohort studies are used for descriptive studies as well as for studies seeking to evaluate comparative effectiveness and/or safety or quality of care. Cohort studies may include only people with exposures (such as to a particular drug or class of drugs) or disease of interest. Cohort studies may also include one or more comparison groups for which data are collected using the same methods during the same period. A single cohort study may in fact include multiple cohorts, each defined by a common disease or exposure. Cohorts may be small, such as those focused on rare diseases, but often they target large groups of people (e.g., in safety studies), such as all users of a particular drug or device. Some limitations of registry-based cohort studies may include limited availability of treatment data and underreporting of outcomes if a patient leaves the registry or is not adequately followed up.[7] These pitfalls should be considered and addressed when planning a study.

6.3. Case-Control

A case-control study gathers patients who have a particular outcome or who have suffered an adverse event ("cases") and "controls" who have not but are representative of the source population from which the cases arise.[8] If properly designed and conducted, it should yield results similar to those expected from a cohort study of the population from which the cases were derived. The case-control design is often employed for understanding the etiology of rare diseases[9] because of its efficiency. In studies where expensive data collection is required, such as some genetic analyses or other sophisticated testing, the case-control design is more efficient and cost-effective than a cohort study because a case-control design collects information only from cases and a sample of noncases. However, if no de novo data collection is required, the use of the cohort design may be preferable since it avoids the challenge of selecting a suitable control group, which may be more susceptible to bias.

Depending on the outcome or event of interest, cases and controls may be identifiable within a single registry. For example, in the evaluation of restenosis after coronary angioplasty in patients with end-stage renal disease, investigators identified both cases and controls from an institutional percutaneous transluminal coronary angioplasty registry; in this example, controls were randomly selected from the registry and matched by age and gender.[10] Alternatively, cases can be identified in the registry and controls chosen from outside the registry. Care must be taken, however, that the controls from outside the registry meet the requirement of arising from the same source population as the cases to which they will be compared. Matching in case-control designs—for example, ensuring that patient characteristics such as age and gender are similar in the cases and their controls—may yield additional efficiency, in that a smaller number of subjects may be required to answer the study question with a given power, but does not eliminate confounding and must be undertaken with care. Matching variables must be accounted for in the analysis, because a form of selection bias similar to confounding will have been introduced by the matching.[11]

Properly executed, a case-control study can add efficiency to a registry if more extensive data are collected by the registry only for the smaller number of subjects selected for the case-control study. This design is sometimes referred to as a "nested" case-control study, since subjects are taken from a larger

cohort. It is generally applied because of budgetary or logistical concerns relating to the additional data desired. Nested case-control studies have been conducted in a wide range of patient registries, from studying the association between oral contraceptives and various types of cancer using the Surveillance Epidemiology and End Results (SEER) program[12 13 14] to evaluating the possible association of depression with Alzheimer's disease. As an example, in the latter case-control study design, probable cases were enrolled from an Alzheimer's disease registry and compared to randomly selected nondemented controls from the same base population.[15]

Case-control studies present special challenges with regard to control selection. More information on considerations and strategies can be found in a set of papers by Wacholder.[16 17 18]

6.4. Case-Cohort

The case-cohort design is a variant of the case-control study. As in a case-control study, a case-cohort study enrolls patients who have a particular outcome or who have suffered an adverse event ("cases") and "controls" who have not, but are representative of the source population from which the cases arise. In nested case-control studies where controls are selected via risk-set sampling, each person in the source population has a probability of being selected as a control that is, ideally, in proportion to his or her person-time contribution to the cohort. In a case-cohort study, however, each control has an equal probability of being sampled from the source population.[19] This allows for collection of pertinent data for cases and for a sample of the full cohort, instead of the whole cohort. For example, in a case-cohort study of histopathologic and microbiological indicators of chorioamnionitis, which included identification of specific microorganisms in the placenta, cases consisted of extreme preterm infants with cerebral palsy. Controls, which can be thought of as a randomly selected subcohort of subjects at risk of the event of interest, were selected from among all infants enrolled in a long-term study of preterm infants.[20] In addition, case-cohort designs allow for the selection of multiple control groups, since controls are selected at the beginning of follow-up.

7. Choosing Patients for Study

The purpose of a registry is to provide information or describe events and patterns, and often to generate hypotheses about a specific patient population to whom study results are meant to apply. Studies can be conducted of people who share common characteristics, with or without the inclusion of comparison groups. For example, studies can be conducted of:

- People with a particular disease/outcome or condition. (These are focused on characteristics of the person.)
  - Examples include studies of the occurrence of cancer or rare diseases, pregnancy outcomes, and recruitment pools for clinical trials.
- Those with a particular exposure. (These exposures may be to a product, procedure, or other health service.)
  - Examples include general surveillance registries, pregnancy registries for particular drug exposures, and studies of exposure to medications and to devices such as stents.[21] They also include studies of people who were treated under a quality improvement program, as well as studies of a particular exposure that requires controlled distribution, such as drugs with serious safety concerns (e.g., isotretinoin, clozapine, natalizumab [Tysabri®]), where the participants in the registry are identified because of their participation in a controlled distribution/risk management program.

- Those who were part of a program evaluation, disease management effort, or quality improvement project.
    - An example is the evaluation of the effectiveness of evidence-based program guidelines on improving treatment.

7.1. Target Population

Selecting patients for registries can be thought of as a multistage process that begins with understanding the target population (the population to which the findings are meant to apply, such as all patients with a disease or a common exposure) and then selecting a sample of this population for study. Some registries will enroll all, or nearly all, of the target population, but most registries will enroll only a sample of the target population. The accessible study population is that portion of the target population to which the participating sites have access. The actual study population is the subset of those who can actually be identified and invited and who agree to participate.[22] While it is desirable for the patients who participate in a study to be representative of the target population, it is rarely possible to study groups that are fully representative from a statistical sampling perspective, either for budgetary reasons or for reasons of practicality. An exception is registries composed of all users of a product (as in post-marketing surveillance studies where registry participation is required as a condition of receiving an intervention), an approach which is becoming more common to manage expensive interventions and/or to track potential safety issues.

There are certain populations that pose greater difficulties in assembling an actual study population that is truly representative of the target population. Children and other vulnerable populations present special challenges in recruitment, as they typically will have more restrictions imposed by institutional review boards (IRBs) and other oversight groups.

As with any research study, very clear definitions of the inclusion and exclusion criteria are necessary and should be well documented, including the rationale for these criteria. A common feature of registries is that they typically have few inclusion and exclusion criteria, which enhances their applicability to broader populations. Restriction, the strategy of limiting eligibility for entry to individuals within a certain range of values for a confounding factor, such as age, may be considered in order to reduce the effect of a confounding factor when it cannot otherwise be controlled, but this strategy may reduce the generalizability of results to other patients.

These criteria will largely be driven by the study objectives and any sampling strategy. For a more detailed description of target populations and their subpopulations, and how these choices affect generalizability and interpretation, see Chapter 13.

Once the patient population has been identified, attention shifts to selecting the institutions and providers from which patients will be selected. For more information on recruiting patients and providers, see Chapter 10.

7.2. Comparison Groups

Once the target population has been selected and the mechanism for their identification (e.g., by providers) is decided, the next decision involves determining whether to collect data on comparators (sometimes called parallel cohorts). Depending on the purpose of the registry, internal, external, or historical groups can be used to strengthen the understanding of whether the observed effects are real and

in fact different from what would have occurred under other circumstances. Comparison groups are most useful in registries where it is important to distinguish between alternative decisions or to assess differences, the magnitude of differences, or the strength of associations between groups. Registries without comparison groups can be used for descriptive purposes, such as characterizing the natural history of a disease or condition, or for hypothesis generation. The addition of a comparison group may add significant complexity, time, and cost to a registry.

Although it may be appealing to use more than one comparison group in an effort to overcome the limitations that may result from using a single group, multiple comparison groups pose their own challenges to the interpretation of registry results. For example, the results of comparative safety and effectiveness evaluations may differ depending on the comparison group used. Generally, it is preferable to make judgments about the "best" comparison group for study during the design phase and then concentrate resources on these selected subjects. Alternatively, sensitivity analyses can be used to test inferences against alternative reference groups to determine the robustness of the findings. (See Chapter 13.5.)

The choice of comparison groups is more complex in registries than in clinical trials. Whereas clinical trials use randomization to try to achieve an equal distribution of known and unknown risk factors that can confound the drug-outcome association, registry studies need to use various design and analytic strategies to control for the confounders that they have measured. The concern for observational studies is that people who receive a new drug or device have different risk factors for adverse events than those who choose other treatments or receive no treatment at all. In other words, the treatment choices are often related to demographic and lifestyle characteristics and the presence of coexisting conditions that affect clinician decisionmaking about whom to treat.[23]

One design strategy that is used frequently to ensure comparability of groups is individual matching of exposed patients and comparators with regard to key demographic factors, such as age and gender. Compatibility is also achieved by inclusion criteria that could, for example, restrict the registry focus to patients who have had the disease for a similar duration or are receiving their first drug treatment for a new condition. These inclusion criteria make the patient groups more similar but may add constraints to the external validity by defining the target population more narrowly. Other design techniques include matching study subjects on the basis of a large number of risk factors, by using statistical techniques (e.g., propensity scoring) to create strata of patients with similar risks. As an example, consider a recent study of a rare side effect in coronary artery surgery for patients with acute coronary syndrome. In this instance, the main exposure of interest was the use of antifibrinolytic agents during revascularization surgery, a practice that had become standard for such surgeries. The sickest patients, who were most likely to have adverse events, were much less likely to be treated with antifibrinolytic agents. To address this, the investigators measured more than 200 covariates (by drug and outcome) per patient and used this information in a propensity score analysis. The results of this large-scale observational study revealed that the traditionally accepted practice (aprotinin) was associated with serious end-organ damage and that the less expensive generic medications were safe alternatives.[24] Incorporation of propensity-scores in analysis is discussed further in Chapter 13.5.

An internal comparison group refers to simultaneous data collection for patients who are similar to the focus of interest (i.e., those with a particular disease or exposure in common), but who do not have the

condition or exposure of interest. For example, a registry might collect information on patients with arthritis who are using acetaminophen for pain control. An internal comparison group could be arthritis patients who are using other medications for pain control. Data regarding similar patients, collected during the same calendar period and using the same data collection methods, are useful for subgroup comparisons, such as for studying the effects in certain age categories or among people with similar comorbidities. However, the information value and utility of these comparisons depend largely on having adequate sample sizes within subgroups, and such analyses may need to be specified a priori to ensure that recruitment supports them. Internal comparisons are particularly useful because data are collected during the same observation period as for all study subjects, which will account for time-related influences that may be external to the study. For example, if an important scientific article is published that affects general clinical practice, and the publication occurs during the period in which the study is being conducted, clinical practice may change. The effects may be comparable for groups observed during the same period through the same system, whereas information from historical comparisons, for example, would be expected to reflect different practices.

An external comparison group is a group of patients similar to those who are the focus of interest, but who do not have the condition or exposure of interest, and for whom relevant data that have been collected outside of the registry are available. For example, the SEER program maintains national data about cancer and has provided useful comparison information for many registries where cancer is an outcome of interest.[25] External comparison groups can provide informative benchmarks for understanding effects observed, as well as for assessing generalizability. Additionally, large clinical and administrative claims databases can contribute useful information on comparable subjects for a relatively low cost. A drawback of external comparison groups is that the data are generally not collected the same way and the same information may not be available. The underlying populations may also be different from the registry population. In addition, plans to merge data from other databases require the proper privacy safeguards to comply with legal requirements for patient data; Chapter 7 covers patient privacy rules in detail.

A historical comparison group refers to patients who are similar to the focus of interest, but who do not have the condition or exposure of interest, and for whom information was collected in the past (such as before the introduction of an exposure or treatment or development of a condition). Historical controls may actually be the same patients who later become exposed, or they may consist of a completely different group of patients. For example, historical comparators are often used for pregnancy studies since there is a large body of population-based surveillance data available, such as the Metropolitan Atlanta Congenital Defects Program (MACDP).[26] This design provides weak evidence because symmetry is not assured (i.e., the patients in different time periods may not be as similar as desired). Historical controls are susceptible to bias by changes over time in uncontrollable, confounding risk factors, such as differences in climate, management practices, and nutrition. Bias stemming from differences in measuring procedures over time may also account for observed differences.

An approach related to the use of historical comparisons is the use of Objective Performance Criteria (OPC) as a comparator. This research method has been described as an alternative to randomized trials, particularly for the study of devices.[27] OPC are "performance criteria based on broad sets of data from historical databases (e.g., literature or registries) that are generally recognized as acceptable values. These criteria may be used for surrogate or clinical endpoints in demonstrating the safety or effectiveness of a

device."[28] A U.S. Food and Drug Administration guidance document on medical devices includes a description of study designs that should be considered as alternatives to randomized clinical trials, and that may meet the statutory criteria for preapproval as well as postapproval evidence.[29] Registries serve as a source of reliable historical data in this context. New registries with safety or effectiveness endpoints may also be planned that will incorporate previously existing OPC as comparators (e.g., for a safety endpoint for a new cardiac device). Such registries might use prior clinical study data to set the "complication-free rate" for comparison.

There are several situations in which conventional prospective design for comparison selection is impossible and a historical comparison may be considered:

- When one cannot ethically continue the use of older treatments or practices, or when clinicians and/or patients refuse to continue their use, so that the researcher cannot identify relevant sites using the older treatments.
- When uptake of a new medical practice has been rapid, concurrent comparisons may differ so markedly from treated patients, in regard to factors related to outcomes of interest, that they cannot serve as valid comparison subjects due to intractable confounding.
- When conventional treatment has been consistently unsuccessful and the effect of new intervention is obvious and dramatic (e.g., first use of a new product for a previously untreatable condition).
- When collecting the comparison data is too expensive.
- When the Hawthorne effect (a phenomenon that refers to changes in the behavior of subjects because they know they are being studied or observed) makes it impossible to replicate actual practice in a comparison group during the same period.
- When the desired comparison is to usual care or "expected" outcomes at a population level, and data collection is too expensive due to the distribution or size of that population.

8. Sampling

Various sampling strategies for patients and sites can be considered. Each of these has tradeoffs in terms of validity and information yield. The representativeness of the sample, with regard to the range of characteristics that are reflective of the broader target population, is often a consideration, but representativeness mainly affects generalizability rather than the internal validity of the results. Representativeness should be considered in terms of patients (e.g., men and women, children, the elderly, different racial or ethnic groups) and sites (academic medical centers, community practices). For sites (health care providers, hospitals, etc.), representativeness is often considered in terms of geography, practice size, and academic or private practice type. Reviewing and refining the research question can help researchers define an appropriate target population and a realistic strategy for subject selection.

To ensure that enough meaningful information will be available for analysis, registry studies often restrict eligibility for entry to individuals within a certain range of characteristics. Alternatively, they may use some form of sampling: random selection, systematic sampling, or a nonrandom approach. Often-used sampling strategies include the following:

- *Probability sampling*: Some form of random selection is used, wherein each person in the population must have a known (often equal) probability of being selected.[30 31 32 33]
- *Census*: A census sample includes every individual in a population or group (e.g., all known cases). A census is not feasible when the group is large relative to the costs of obtaining information from individuals.

- *Simple random sampling*: The sample is selected in such a way that each person has the same probability of being sampled.
- *Stratified random sampling*: The group from which the sample is to be taken is first stratified into subgroups on the basis of an important, related characteristic (e.g., age, parity, weight) so that each individual in a subgroup has the same probability of being included in the sample, but the probabilities for different subgroups or strata are different. Stratified random sampling ensures that the different categories of characteristics that are the basis of the strata are sufficiently represented in the sample. However, the resulting data must be analyzed using more complicated statistical procedures (such as Mantel-Haenszel) in which the stratification is taken into account.
- *Systematic sampling*: Every nth person in a population is sampled.
- *Cluster (area) sampling*: The population is divided into clusters, these clusters are randomly sampled, and then some or all patients within selected clusters are sampled. This technique is particularly useful in large geographic areas or when cluster-level interventions are being studied.
- *Multistage sampling*: Multistage sampling can include any combination of the sampling techniques described above.
- *Nonprobability sampling*: Selection is systematic or haphazard but not random. The following sampling strategies affect the type of inferences that can be drawn; for example, it would be preferable to have a random sample if the goal were to estimate the prevalence of a condition in a population. However, systematic sampling of "typical" patients can generate useful data for many purposes, and is often used in situations where probability sampling is not feasible.[34]
- *Case series or consecutive (quota) sampling*: All consecutive eligible patients treated at a given practice or by a given clinician are enrolled until the enrollment target is reached. This approach is intended to reduce conscious or unconscious selection bias on the part of clinicians as to whom to enroll in the study, especially with regard to factors that may be related to prognosis.
- *Haphazard, convenience, volunteer, or judgmental sampling*: This includes any sampling not involving a truly random mechanism. A hallmark of this form of sampling is that the probability that a given individual will be in the sample is unknown before sampling. The theoretical basis for statistical inference is lost, and the result is inevitably biased in unknown ways.
- *Modal instance*: The most typical subject is sampled.
- *Purposive*: Several predefined groups are deliberately sampled.
- *Expert*: A panel of experts judges the representativeness of the sample or is the source that contributes subjects to a registry.

Individual matching of cases and controls is sometimes used as a sampling strategy for controls. Controls are matched with individual cases who have similar confounding factors, such as age, to reduce the effect of the confounding factors on the association being investigated.

Patients may be recruited in a fashion that allows for individual matching. For example, if a 69-year-old "case" participates in the registry, a control near in age will be sought. Individual matching for prospective recruitment is challenging and not customarily used. More often, matching is used to create subgroups for supplemental data collection for case-control studies and cohort studies when subjects are limited and/or stratification is unlikely to provide enough subjects in each stratum for meaningful evaluation.

There are a number of other sampling strategies that have arisen from survey research (e.g., snowball, heterogeneity), but they are of less relevance to registries.

9. Registry Size and Duration

Precision in measurement and estimation corresponds to the reduction of random error; it can be improved by increasing the size of the study and modifying the design of the study to increase the efficiency with which information is obtained from a given number of subjects.[30]

During the registry design stage, it is critical to explicitly state how large the registry will be, how long patients should be followed, and what the justifications are for these decisions. These decisions are based on the overall purpose of the registry. For example, in addressing specific questions of product safety or effectiveness, the desired level of precision to confirm or rule out the existence of an important effect should be specified, and ideally should be linked to policy or practice decisions that will be made based on the evidence. For registries with aims that are descriptive or hypothesis generating, study size may be arrived at through other considerations.

The duration of registry enrollment and followup should be determined both by required sample size (number of patients or person-years to achieve the desired power) and by time-related considerations. The induction period for some outcomes of interest must be considered, and sufficient followup time allowed for the exposure under study to have induced or promoted the outcome. Biological models of disease etiology and causation usually indicate the required time period of observation for an effect to become apparent. Calendar time may be a consideration in studies of changes in clinical practice or interventions that have a clear beginning and end. The need for evidence to inform policy may also determine a timeframe within which the evidence must be made available to decisionmakers.

A detailed discussion of the topic of sample size calculations for registries is provided in Appendix A. For present purposes it is sufficient to briefly describe some of the critical inputs to these calculations that must be provided by the registry developers:

- The expected timeframe of the registry and the time intervals at which analyses of registry data will be performed.
- Either the size of clinically important effects (e.g., minimum clinically important differences) or the desired precision associated with registry-based estimates.
- Whether or not the registry is intended to support regulatory decisionmaking. If the results from the registry will affect regulatory action—for example, the likelihood that a product may be pulled from the market—then the precision of the overall risk estimate is important, as is the necessity to predict and account for attrition.

In a classical calculation of sample size, the crucial inputs that must be provided by the investigators include either the size of clinically important effects or their required precision. For example, suppose that the primary goal of the registry is to compare surgical complication rates in general practice with those in randomized trials. The inputs to the power calculations would include the complication rates from the randomized trials (e.g., 4 percent) and the complication rate in general practice, which would reflect a meaningful departure from this rate (e.g., 6 percent). If, on the other hand, the goal of the registry is simply to track complication rates (and not to compare the registry with an external standard), then the investigators should specify the required width of the confidence interval associated with those rates. For example, in a large registry, the 95-percent confidence interval for a 5-percent complication rate might extend from 4.5 percent to 5.5 percent. If all of the points in this confidence interval lead to the same

decision, then an interval of ±0.5 percent is considered sufficiently precise, and this is the input required for the estimation of sample size.

Specifying the above inputs to sample size calculations is a substantial matter and usually involves a combination of quantitative and qualitative reasoning. The issues involved in making this specification are essentially similar for registries and other study designs, though for registries designed to address multiple questions of interest, one or more primary objectives or endpoints must be selected that will drive the selection of a minimum sample size to meet those objectives.

Other considerations that should sometimes be taken into account when estimating sample sizes include:

- whether individual patients can be considered "independent" or share factors that would lead to correlation in measures between them;
- whether multiple comparisons are being made and subjected to statistical testing; and
- whether levels of expected attrition or lack of adherence to therapy may require a larger number of patients to achieve the desired number of person-years of followup or exposure.

In some cases, patients under study who share some group characteristics, such as patients treated by the same clinician or practice, or at the same institution, may not be entirely independent from one another with regard to some outcomes of interest or when studying a practice-level intervention. To the extent they are not independent, a measure of interdependence, the intraclass correlation (ICC), and so-called "design effect" must be considered in generating the overall sample size calculation. A reference addressing sample size considerations for a study incorporating a cluster-randomized intervention is provided.[35] A hierarchical or multilevel analysis may be required to account for one or more levels of "grouping" of individual patients, discussed further in Chapter 13.5. One approach to addressing multiple comparisons in the surgical complication rate example above is to use control chart methodology, a statistical approach used in process measurement to examine the observed variability and determine whether out-of-control conditions are occurring. Control chart methodology is also used in sample size estimation, largely for studies with repeated measurements, to adjust the sample size as needed and therefore maintain reasonably precise estimates of confidence limits around the point estimate. Accordingly, for registries that involve ongoing evaluation, sample size per time interval could be determined by the precision associated with the related confidence interval, and decision rules for identifying problems could then be based on control chart methodology.

Although most of the emphasis in estimating study size requirements is focused on patients, it is equally important to consider the number of sites needed to recruit and retain enough patients to achieve a reasonably informative number of person-years for analysis. Many factors are involved in estimating the number of sites needed for a given study, including the number of eligible patients seen in a given practice during the relevant time period, desired representativeness of sites with regard to geography, practice size, or other features, and the timeframe within which study results are required, which may also limit the timeframe for patient recruitment.

In summary, the aims of a registry, the desired precision of information sought, and the hypotheses to be tested, if any, determine the process and inputs for arriving at a target sample size and specifying the duration of followup. Registries with mainly descriptive aims, or those that provide quality metrics for clinicians or medical centers, may not require the choice of a target sample size to be arrived at through

power calculations. In either case, the costs of obtaining study data, in monetary terms and in terms of researcher, clinician, and patient time and effort, may set upper as well as lower limits on study size. Limits to study budgets and the number of sites and patients that could be recruited may be apparent at the outset of the study. However, an underpowered study involving substantial data collection that is ultimately unable to satisfactorily answer the research question(s) may prove to be a waste of finite monetary as well as human resources that could better be applied elsewhere.

10. Internal and External Validity

The potential for bias refers to opportunities for systematic errors to influence the results. Internal validity is the extent to which study results are free from bias, and the reported association between exposure and outcome is not due to unmeasured or uncontrolled-for variables. Generalizability, also known as external validity, is a concept that refers to the utility of the inferences for the broader population that the study subjects are intended to represent. In considering potential biases and generalizability, we discuss the differences between RCTs and registries, since these are the two principal approaches to conducting clinically relevant prospective research.

The strong internal validity that earns RCTs high grades for evidence comes largely from the randomization of exposures that helps ensure that the groups receiving the different treatments are similar in all measured or unmeasured characteristics, and that, therefore, any differences in outcome (beyond those attributable to chance) can be reasonably attributed to differences in the efficacy or safety of the treatments. However, it is worth noting that RCTs are not without their own biases, as illustrated by the "intent-to-treat" analytic approach, in which people are considered to have used the assigned treatment, regardless of actual compliance. The intent-to-treat analyses can minimize a real difference, known as bias toward the null, by including the experience of people who adhered to the recommended study product along with those who did not.

Another principal difference between registries and RCTs is that RCTs are often focused on a relatively homogeneous pool of patients from which significant numbers of patients are purposefully excluded at the cost of external validity—that is, generalizability to the target population of disease sufferers. Registries, in contrast, usually focus on generalizability so that their population will be representative and relevant to decision makers.

10.1. Generalizability

The strong external validity of registries is achieved by the fact that they include typical patients, which often include more heterogeneous populations than those participating in RCTs (e.g., wide variety of age, ethnicity, and comorbidities). Therefore, registry data can provide a good description of the course of disease and impact of interventions in actual practice and, for some purposes, may be more relevant for decisionmaking than the data derived from the artificial constructs of the clinical trial. In fact, even though registries have more opportunities to introduce bias (systematic error) because of their nonexperimental methodology, well-designed observational studies can approximate the effects of interventions observed in RCTs on the same topic[36 37] and, in particular, in the evaluation of health care effectiveness in many instances.[38]

The choice of groups from which patients will be selected directly affects generalizability. No particular method will ensure that an approach to patient recruitment is adequate, but it is worthwhile to note that the way in which patients are recruited, classified, and followed can either enhance or diminish the

external validity of a registry. Some examples of how these methods of patient recruitment and followup can lead to systematic error follow.

10.2. Information Bias

If the registry's principal goal is the estimation of risk, it is possible that adverse events or the number of patients experiencing them will be underreported if the reporter will be viewed negatively for reporting them. It is also possible for those collecting data to introduce bias by misreporting the outcome of an intervention if they have a vested interest in doing so. This type of bias is referred to as information bias (also called detection, observer, ascertainment, or assessment bias), and it addresses the extent to which the data that are collected are valid (represent what they are intended to represent) and accurate. This bias arises if the outcome assessment can be interfered with, intentionally or unintentionally. On the other hand, if the outcome is objective, such as whether or not a patient died or the results of a lab test, then the data are unlikely to be biased.

10.3. Selection Bias

A registry may create the incentive to enroll only patients who either are at low risk of complications or who are known not to have suffered such complications, biasing the results of the registry toward lower event rates. Those registries whose participants derive some sort of benefit from reporting low complication rates, for example, surgeons participating in registries, are at particularly high risk for this type of bias. Another example of how patient selection methods can lead to bias is the use of patient volunteers, a practice that may lead to selective participation from subjects most likely to perceive a benefit, distorting results for studies of patient-reported outcomes.

Enrolling patients who share a common exposure history, such as having used a drug that has been publicly linked to a serious adverse effect, could distort effect estimates for cohort and case-control analyses. Registries can also selectively enroll people who are at higher risk of developing serious side effects, since having a high-risk profile can motivate a patient to participate in a registry.

The term *selection bias* refers to situations where the procedures used to select study subjects lead to an effect estimate among those participating in the study that is different from the estimate that is obtainable from the target population.[39] Selection bias may be introduced if certain subgroups of patients are routinely included or excluded from the registry.

10.4. Channeling Bias (Confounding by Indication)

Channeling bias, also called confounding by indication, is a form of selection bias where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences.[40] For example, physicians may prescribe new treatments more often to those patients who have failed on traditional first-line treatments.

One approach to designing studies to address channeling bias is to conduct a prospective review of cases, in which external reviewers are blinded as to the treatments that were employed and are asked to determine whether a particular type of therapy is indicated and to rate the overall prognosis for the patient.[41] This method of blinded prospective review was developed to support research on ruptured cerebral aneurysms, a rare and serious situation. The results of the blinded review were used to create risk strata for analysis so that comparisons could be conducted only for candidates for whom both therapies

under study were indicated, a procedure much like the application of additional inclusion and exclusion criteria in a clinical trial.

A computed "propensity score" (i.e., the predicted probability of use of one therapy over another based on medical history, health care utilization, and other characteristics measured prior to the initiation of therapy) is increasingly incorporated into study designs to address this type of confounding.[42 43] Propensity scores may be used to create cohorts of initiators of two different treatments matched with respect to probability of use of one of the two therapies, for stratification, or for inclusion as a covariate in a multivariate analysis. Studies incorporating propensity scores as part of their design may be planned prior to and implemented shortly following launch of a new drug as part of a risk management program, with matched comparators being selected over time, so that differences in prescribing patterns following drug launch may be taken into account.[44]

Instrumental variables, or factors strongly associated with treatment but related to outcome only through their association with treatment, may provide additional means of adjustment for confounding by indication, as well as unmeasured confounding.[45] Types of instrumental variables include providers' preferences for one therapy over another, which exploit variation in practice as a type of natural experiment, variation or changes in insurance coverage or economic factors (e.g., cigarette taxes) that are associated with an exposure, or geographic distance from a specific type of service.[46 47] Variables that serve as effective instruments of this nature are not always available and may be difficult to identify. While use of clinician or study site may, in some specific cases, offer potential as an instrumental variable for analysis, the requirement that use of one therapy over another be very strongly associated with the instrument is often difficult to meet in real-world settings. In most cases, instrumental variable analysis provides an alternative for secondary analysis of study data. Instrumental variable analysis either may support the conclusions drawn on the basis of the initial analysis, or it may raise additional questions regarding the potential impact of confounding by indication.[43]

In some cases, however, differences in disease severity or prognosis between patients receiving one therapy rather than another may be so extreme and/or unmeasurable that confounding by indication is not remediable in an observational design.[48] This represents special challenges for observational studies of comparative effectiveness, as the severity of underlying illness may be a strong determinant of both choice of treatment and treatment outcome.

10.5. Bias from Study of Existing Rather Than New Product Users

If there is any potential for tolerance to affect the use of a product, such that only those who perceive benefit from it or are free from harm continue using it, the recruitment of existing users rather than new users may lead to the inclusion of only those who have tolerated or benefited from the intervention, and would not necessarily capture the full spectrum of experience and outcomes. Selecting only existing users may introduce any number of biases, including incidence/prevalence bias, survivorship bias, and followup bias. By enrolling new users (an inception or incidence cohort), a study ensures that the longitudinal experience of all users will be captured, and that the ascertainment of their experience and outcomes will be comparable.[49]

10.6. Loss to Followup

Loss to followup or attrition of patients and sites threatens generalizability as well as internal validity if there is differential loss; for example, loss of participants with a particular exposure or disease, or with

particular outcomes. Loss to followup and attrition are generally a serious concern only when they are nonrandom (that is, when there are systematic differences between those who leave or are lost and those who remain). The magnitude of loss to followup or attrition determines the potential impact of any bias. Given that the differences between patients who remain enrolled and those who are lost to followup are often unknown (unmeasurable), preventing loss to followup in long-term studies to the fullest extent possible will increase the credibility and validity of the results.[50] Attrition should be considered with regard to both patients and study sites, as results may be biased or less generalizable if only some sites (e.g., teaching hospitals) remain in the study while others discontinue participation.

10.7. Assessing the Magnitude of Bias

Remaining alert for any source of bias is important, and the value of a registry is enhanced by its ability to provide a formal assessment of the likely magnitude of all potential sources of bias. Any information that can be generated regarding nonrespondents, missing respondents, and the like, is helpful, even if it is just an estimation of their raw numbers. As with many types of survey research, an assessment of differential response rates and patient selection can sometimes be undertaken when key data elements are available for both registry enrollees and nonparticipants. Such analyses can easily be undertaken when the initial data source or population pool is that of a health care organization, employer, or practice that has access to data in addition to key selection criteria (e.g., demographic data or data on comorbidities). Another tool is the use of sequential screening logs, in which all subjects fitting the inclusion criteria are enumerated and a few key data elements are recorded for all those who are screened. This technique allows some quantitative analysis of nonparticipants and assessments of the effects, if any, on representativeness. Whenever possible, quantitative assessment of the likely impact of bias is desirable to determine the sensitivity of the findings to varying assumptions. A recent text on quantitative analysis of bias through validation studies, and on probabilistic approaches to data analysis, provides a guide for planning and implementing these methods.[51]

Qualitative assessments, although not as rigorous as quantitative approaches, may give users of the research a framework for drawing their own conclusions regarding the effects of bias on study results if the basis for the assessment is made explicit in reporting the results.

Accordingly, two items that can be reported to help the user assess the generalizability of research results based on registry data are a description of the criteria used to select the registry sites, and the characteristics of these sites, particularly those characteristics that might have an impact on the purpose of the registry. For example, if a registry designed for the purpose of assessing adherence to lipid screening guidelines requires that its sites have a sophisticated electronic medical record in order to collect data, it will probably report better adherence than usual practice because this same electronic medical record facilitates the generation of real-time reminders to engage in screening. In this case, a report of rates of adherence to other screening guidelines (for which there were no reminders), even if these are outside the direct scope of inquiry, would provide some insight into the degree of overestimation.

Finally, and most importantly, whether or not study subjects need to be evaluated on their representativeness depends on the purpose and kind of inference needed. For example, for understanding biological effects, it is not necessary to sample in proportion to the underlying distribution in the population. It is more important to demonstrate to the stakeholders the degree to which patients who are included in a registry are representative of the population from which they were derived.

11. Summary

In summary, the key points to consider in designing a registry include study design, data sources, patient selection, comparison groups, sampling strategies, and considerations of possible sources of bias and ways to address them to the extent that is practical and achievable.

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Case Examples for Chapter 3

Case Example 2. Designing a Registry for a Health Technology Assessment

Description	The Nuss procedure registry was a short-term registry designed specifically for the health technology assessment of the Nuss procedure, a novel, minimally invasive procedure for the repair of pectus excavatum, a congenital malformation of the chest. The registry collected procedure outcomes, patient-reported outcomes, and safety outcomes.
Sponsor	National Institute for Health and Clinical Excellence (NICE), United Kingdom
Year Started	2004
Year Ended	2007
No. of Sites	13 hospitals
No. of Patients	260

Challenge

The Nuss procedure is a minimally invasive intervention for the repair of pectus excavatum. During a review of the evidence supporting this procedure conducted in 2003, the National Institute for Health and Clinical Excellence (NICE) determined that the existing data included relatively few patients, few quality of life outcomes, and did not sufficiently address safety concerns. NICE concluded in the 2003 review that the evidence was not adequate for routine use and that more evidence was needed to make a complete assessment of the procedure.

Proposed Solution

Gathering additional evidence through a randomized controlled trial was not feasible for several reasons. First, a blinded trial would be difficult because the other procedures for the repair of pectus excavatum produce much larger scars than the Nuss procedure. Surgeons also tend to perform either only the Nuss procedure or only another procedure, a factor that would complicate randomization efforts. In addition, only a small number of procedures are done in the United Kingdom. The sample for a randomized trial would likely be very small, making it difficult to detect rare adverse events.

Due to these limitations, NICE decided to develop a short-term registry to gather evidence on the Nuss procedure. The advantages of a registry were its ability to gather data on all patients undergoing the procedure in the UK to provide a more complete safety assessment, and its ability to collect patient-reported outcomes.

The registry was developed by an academic partner, with input from clinicians. Hospitals performing the procedure were identified and asked to enter data into the registry on all patients undergoing the intervention. Once the registry was underway, the cases in the registry were compared against cases included in the Hospital Episodes Statistics (HES) database, a nationwide source of routine data on hospital activity, and nonparticipating hospitals were identified and prompted to enter their data.

Results

NICE conducted a reassessment of the Nuss procedure in 2009, comparing data from the registry to other published evidence on safety and efficacy. The quantity of published literature had increased substantially between 2003 and 2009. The new publications primarily focused on technical and safety outcomes, while the registry included patient-reported outcomes. The literature and the registry reported similar rates of major adverse events such as bar displacement (from 2 to 10 percent). Based on the registry data and the new literature, the review committee found that the evidence was now sufficient to support routine use of the Nuss procedure, and no further review of the guidance is planned. Committee members considered that the registry made a useful contribution to guidance development.

Key Point

The Nuss registry demonstrated that a small, short-term, focused registry with recommended (but not automatic or mandatory) submission can produce useful data, both about safety and about patient-reported outcomes.

Case Example 3. Developing Prospective Nested Studies in Existing Registries

Description	The Consortium of Rheumatology Researchers of North America (CORRONA) is a national disease registry of patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA).
Sponsor	CORRONA Investigators and Genentech
Year Started	2001
Year Ended	Ongoing
No. of Sites	Over 100 sites in the United States
No. of Patients	As of March 31 2012: 36,922 (31,701 RA patients and 5,221 PsA patients).

Challenge

In 2001, the CORRONA data collection program was established to collect physician- and patient-reported, longitudinal effectiveness and safety data for the treatment and management of RA and PsA. Any patient with RA or PsA upon diagnosis can participate in the registry, and participation in the registry is life-long unless the patient withdraws consent. With an existing infrastructure and its representative, real-world nature, the disease registry can be used as a robust opportunity for nested trials at sites that have been trained in data collection and verification.

Proposed Solution

In collaboration with Genentech, the CORRONA investigators are utilizing the registry in two separate prospective, nested sub-studies: the Comparative Effectiveness Registry to study Therapies for Arthritis and Inflammatory CoNditions (CERTAIN) and the Treat to Target (T2T) study. Based on the study

eligibility criteria and the capabilities of CORRONA sites, different patients and sites are being selected to participate in CERTAIN and T2T.

The CERTAIN study is a nested comparative effectiveness and safety study evaluating real-world differences in classes of biologic agents among RA patients initiating either tumor necrosis factor (TNF) antagonists or non-TNF inhibitor biologic agents. The study is enrolling approximately 2,750 patients over three years to address comparative effectiveness questions. Long-term safety follow-up data will be collected through life-long patient participation in the CORRONA registry after CERTAIN study completion. Data are collected at mandated 3-month intervals and include standard validated physician- and patient-derived outcomes and centrally-processed laboratory measures such as complete blood counts, metabolic panel, high sensitivity CRP, lipids with direct (nonfasting) LDL, immunoglobulin levels and serology (CCP and RF). Serum, plasma, DNA and RNA will be stored for future research. In addition, adverse event data are being obtained with inclusion of primary "source" documents, followed by a robust process of verification and adjudication.

The T2T study is a cluster-randomized, open-label study comparing treatment acceleration (i.e., monthly visits with a change in therapeutic agent, dosage or route of administration in order to achieve a target metric of disease activity) against usual care (i.e., no mandated changes to therapy or visit frequencies beyond what the treating physician considers appropriate for the patient). This study will attempt to determine both the feasibility and outcomes of treating to target in a large U.S. population. This one-year study is enrolling 888 patients. Data collection includes standard measures of disease activity such as Clinical-Disease Activity Index (CDAI) score, Disease Activity Score-28 (DAS28), and Routine Assessment of Patient Index Data-3 (RAPID 3), as well as rates of acceleration, frequency of visits, and suspected RA drug-related toxicities. The purpose of the trial is to test the hypothesis that accelerated aggressive therapy of RA correlates with better long-term patient outcomes.

Results

The CERTAIN and T2T studies, now in the enrollment phase, exemplify the key advantages and the unique operational synergies of successfully nesting studies within an existing disease registry. This design approach has the advantage of minimizing the usual study start-up and implementation challenges. The registry allows real-time identification of eligible patients typically seen in a U.S. clinical practice, which can facilitate patient recruitment. Both CERTAIN and T2T have broad inclusion criteria to increase representativeness of the population enrolled. Established registry sites include investigators, staff, and patients already experienced with the registry questionnaires and research activities.

The two nested sub-studies require additional patient consent and site reimbursement, as they collect blood samples that increase the time required to complete a study visit. CORRONA collaborates with an academic institution to collect personal identifiers and patient consent to release medical records. This will facilitate verification of serious adverse event for patients participating in CERTAIN. While this feature adds value to CERTAIN's ability to address long-term safety questions, it entailed establishing a new mechanism to ensure that the two databases (CORRONA and a database for personal identifiers) remain separate from each other in a highly secure way. New enrollment and screening instructions

were developed for each substudy with mandated completion of required training for participating physicians and research coordinators.

Key Point

Designing a prospective, nested study within an established disease registry has many benefits, including leveraging existing infrastructure, patient and site staff familiarity with the registry, and site relationships. Sub-studies need to be well planned and address a compelling clinical issue. Registry personnel must provide sufficient guidance, instructions, and rationale to sites in order to ensure that the transition and distinction from core registry operations is accomplished in smooth manner in order to achieve the goal of high quality research.

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Case Example 4. Designing a Registry to Address Unique Patient Enrollment Challenges

Description	The Anesthesia Awareness Registry is a survey-based registry that collects detailed data about patient experiences of anesthesia awareness. Patient medical records are used to assess anesthetic factors associated with the patient's experience. An optional set of psychological assessment instruments measure potential trauma-related sequelae including depression and post-traumatic stress disorder (PTSD).
Sponsor	American Society of Anesthesiologists
Year Started	2007
Year Ended	Ongoing
No. of Sites	Not applicable
No. of Patients	265

Challenge

Anesthesia awareness is a recognized complication of general anesthesia, defined as the unintended experience and explicit recall of events during surgery. The incidence of anesthesia awareness has been estimated at 1-2 patients per 1000 anesthetics and may result in development of serious and long-term psychological sequelae including PTSD. The causes and preventive strategies have been studied, and there is disagreement in the scientific community about the effectiveness of monitoring devices for prevention of anesthesia awareness.

The population of patients experiencing anesthesia awareness is difficult to identify. Although standard short questionnaires designed to identify anesthesia awareness are sometimes administered to patients post-operatively, many patients experience delayed recollection and do not realize that they were awake during their procedure until several weeks later. These patients may or may not report their experience back to their provider. In addition, because of the often unsettling and traumatic nature of their experience, even patients who recognize their anesthesia awareness before being discharged from the hospital may not feel comfortable reporting it to their surgeon or other healthcare providers.

With ongoing coverage in the media, anesthesiologists faced increasing concern and fear about anesthesia awareness among their patients. The American Society of Anesthesiologists sought a patient-oriented approach to this problem.

Proposed Solution

Because this population of patients is not always immediately recognized in the healthcare setting, the registry was created to collect case reports of anesthesia awareness directly from patients. A patient advocate was invited to consult in the registry's development and provides ongoing advice from the patient perspective. The registry hosts a website that provides information about anesthesia awareness and directions for enrolling in the registry. Any patient who believes they have experienced anesthesia awareness may voluntarily submit a survey and medical records to the registry. Psychological assessments are optional. An optional open-ended discussion about the patient's anesthesia awareness experience provides patients with an opportunity to share information that may not be elicited through the survey.

Results

The registry has enrolled 265 patients since 2007. Patients who enroll are self-selected, and the sample is likely biased towards patients with emotional sequelae. While the information provided to potential enrollees clearly states that eligibility is restricted to awareness during general anesthesia, a surprising number of enrollments involve patients who were intended to be awake during regional anesthesia or sedation. This revealed a different side to the problem of anesthesia awareness: clearly, some patients did not understand the nature of the anesthetic that would be provided for their procedure, or patients had expectations that were not met by their anesthesia providers. Most enrollees experienced long-term psychological sequelae, regardless of anesthetic technique.

Key Point

Allowing the registry's purpose to drive its design produces a registry that is responsive to the expected patient population. Employing direct-to-patient recruitment can be an effective way of reaching a patient population that otherwise would not be enrolled in the registry, which can yield surprising and important insights into patient experience.

For More Information

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Chapter 4. Data Elements for Registries

1. Introduction

Selection of data elements for a registry requires a balancing of potentially competing considerations. These considerations include the importance of the data elements to the integrity of the registry, their reliability, their necessity for the analysis of the primary outcomes, their contribution to the overall response burden, and the incremental costs associated with their collection. Registries are generally designed for a specific purpose, and data elements that are not critical to the successful execution of the registry or to the core planned analyses should not be collected unless there are explicit plans for their analysis.

The selection of data elements for a registry begins with the identification of the domains that must be quantified to accomplish the registry purpose. The specific data elements can then be selected, with consideration given to clinical data standards, common data definitions, and the use of patient identifiers. Next, the data element list can be refined to include only those elements that are necessary for the registry purpose. Once the selected elements have been incorporated into a data collection tool, the tool can be pilot tested to identify potential issues, such as the time required to complete the form, data that may be more difficult to access than realized during the design phase, and practical issues in data quality (such as appropriate range checks). This information can then be used to modify the data elements and reach a final set of elements.

2. Identifying Domains

Registry design requires explicit articulation of the goals of the registry and close collaboration among disciplines, such as epidemiology, health outcomes, statistics, and clinical specialties. Once the goals of the study are determined, the domains most likely to influence the desired outcomes must be defined. Registries generally include personal, exposure, and outcomes information. The personal domain consists of data that describe the patient, such as information on patient demographics, medical history, health status, and any necessary patient identifiers. The exposure domain describes the patient's experience with the product, disease, device, procedure, or service of interest to the registry. Exposure can also include other treatments that are known to influence outcome but are not necessarily the focus of the study, so that their confounding influence can be adjusted for in the planned analyses. The outcomes domain consists of information on the patient outcomes that are of interest to the registry; this domain should include both the primary endpoints and any secondary endpoints that are part of the overall registry goals.

In addition to the goals and desired outcomes, it is necessary to consider the need to create important subsets when defining the domains. Measuring potential confounding factors (variables that are linked with both the exposure and outcome) should be taken into account in this stage of registry development. Collecting data on potential confounders will allow for analytic or design control. (See Chapters 3 and 13.)

Understanding the time reference for all variables that can change over time is critical in order to distinguish cause-and-effect relationships. For example, a drug taken after an outcome is observed cannot possibly have contributed to the development of that outcome. Time reference periods can be addressed by including start and stop dates for variables that can change; they can also be addressed categorically, as

is done in some quality improvement registries. For example, the Paul Coverdell National Acute Stroke Registry organized its patient-level information into categories to reflect the timeframe of the stroke event from onset through treatment to followup. In this case, the domains were categorized as prehospital, emergency evaluation and treatment, in-hospital evaluation and treatment, discharge information, and postdischarge followup.[1]

3. Selecting Data Elements

Once the domains have been identified, the process of selecting data elements begins with identification of the data elements that best quantify that domain and the source(s) from which those data elements can be collected. When selecting data elements, gaining consensus among the registry stakeholders is important, but this must be achieved without undermining the purpose of the registry by including elements solely to please a stakeholder. Each data element should support the purpose of the registry and answer an explicit scientific question or address a specific issue or need. The most effective way to select data elements is to start with the study purpose and objective, and then decide what types of groupings, measurements, or calculations will be needed to analyze that objective. Once the plan of analysis is clear, it is possible to work backward to define the data elements necessary to implement that analysis plan. This process keeps the group focused on the registry purpose and limits the number of extraneous ("nice to know") data elements that may be included.[2] (See Case Example 5.)

The data element selection process can be simplified if clinical data standards for a disease area exist. While there is a great need for common core datasets for conditions, currently there are few consensus or broadly accepted sets of standard data elements and data definitions for most disease areas. Thus, different studies of the same disease state may use different definitions of fundamental concepts, such as the diagnosis of myocardial infarction or the definition of worsening renal function.

To address this problem and to support more consistent data elements so that comparisons across studies can be more easily accomplished, some specialty societies and organizations are beginning to compile clinical data standards. For example, the American College of Cardiology (ACC) has created clinical data standards for acute coronary syndromes, heart failure, and atrial fibrillation.[3] [4] [5] These are used by registries such as the National Cardiovascular Data Registry (NDCR®) ICD Registry™, which derived their publically posted data elements and definitions from the ACC/AHA Key Data Elements and Definitions for Electrophysiological Studies and Procedures.[6] The National Cancer Institute (NCI) provides the Cancer Data Standards Registry and Repository (caDSR), which includes the caBIG® (Cancer Biomedical Informatics Grid®)-NCI data standards and the Cancer Therapy Evaluation Program (CTEP) common data element initiative.[7,8] The North American Association of Central Cancer Registries (NAACCR) has developed a set of standard data elements and a data dictionary, and it promotes and certifies the use of these standards.[9] The American College of Surgeons National Cancer Database (NCDB) considers its data elements to be nationally standardized and open source.[10]

To a lesser extent, other disease areas also have begun to catalog data element lists and definitions. In the area of trauma, the International Spinal Cord Society has developed an International Spinal Cord Injury Core dataset to facilitate comparison of studies from different countries,[11] and the National Center for Injury Prevention and Control has developed Data Elements for Emergency Department Systems (DEEDS), which are uniform specifications for data entered into emergency department patient records.[12] In the area of neurological disorders, the National Institute of Neurological Disorders and Stroke

(NINDS) maintains a list of several hundred data elements and definitions (Common Data Elements).[13] In the area of infection control, the National Vaccine Advisory Committee (NVAC) approved a new set of core data elements for immunization information systems in 2007, which are used as functional standards by groups such as the American Immunization Registry Association (AIRA).[14,15] Currently, there are more than one set of lists for some conditions (e.g., cancer) and no central method to search broadly across disease areas.

Some standards organizations are also working on core datasets. The Clinical Data Interchange Standards Consortium (CDISC) Clinical Data Acquisition Standards Harmonization (CDASH) is a global, consensus-based effort to recommend minimal datasets in 16 domains. While developed primarily for clinical trials, these domains have significant utility for patient registries. They currently comprise adverse events, comments, prior and concomitant medications, demographics, disposition, drug accountability, electrocardiogram test results, exposure, inclusion and exclusion criteria, laboratory test results, medical history, physical examination, protocol deviations, subject characteristics, substance abuse, and vital signs. The CDASH Standards information also includes a table on best practices for developing case report forms.[16]

The use of established data standards, when available, is essential so that registries can maximally contribute to evolving medical knowledge. Standard terminologies—and to a greater degree, higher level groupings into core datasets for specific conditions—not only improve efficiency in establishing registries but also promote more effective sharing, combining, or linking of datasets from different sources. Furthermore, the use of well-defined standards for data elements and data structure ensures that the meaning of information captured in different systems is the same. This is critical for "semantic" interoperability between information systems, which will be increasingly important as health information system use grows. This is discussed more in Chapter 15.6.2.

Clinical data standards are important to allow comparisons between studies, but when different sets of standards overlap (i.e., are not harmonized), the lack of alignment may cause confusion during analyses. To consolidate and align standards that have been developed for clinical research, CDISC, the HL7 (Health Level 7) Regulated Clinical Research Information Management Technical Committee (RCRIM TC), NCI, and the U.S. Food and Drug Administration (FDA) have collaborated to create the Biomedical Research Integrated Domain Group (BRIDG) model. The purpose of this project is to provide an overarching model that can be used to harmonize standards between the clinical research domain and the health care domain. BRIDG is a domain analysis model (DAM), meaning that it provides a common representation of the semantics of protocol-driven clinical and preclinical research, along with the associated data, resources, rules, and processes used to formally assess a drug, treatment, or procedure.[17] The BRIDG model is freely available to the public as part of an open-source project at www.bridgemodel.org. It is hoped that the BRIDG model will guide clinical researchers in selecting approaches that will enable their data to be compared with other clinical data, regardless of the study phase or data collection method.[18]

In cases where clinical data standards for the disease area do not exist, established datasets may be widely used in the field. For example, United Network of Organ Sharing (UNOS) collects a large amount of data on organ transplant patients. Creators of a registry in the transplant field should consider aligning their

data definitions and data element formats with those of UNOS to simplify the training and data abstraction process for sites.

Other examples of widely used datasets are the Joint Commission and the Centers for Medicare & Medicaid Services (CMS) data elements for hospital data submission programs. These datasets cover a range of procedures and diseases, from heart failure and acute myocardial infarction to pregnancy and surgical infection prevention. Hospital-based registries that collect data on these conditions may want to align their datasets with the Joint Commission and CMS. However, one limitation of tying elements and definitions to another data collection program rather than a fixed standard is that these programs may change their elements or definitions. With Joint Commission core measure elements, for example, this has occurred with some frequency.

If clinical data standards for the disease area and established datasets do not exist, it is still possible to incorporate standard terminology into a registry. This will make it easier to compare the registry data with the data of other registries and reduce the training needs and data abstraction burden on sites. Examples of several standard terminologies used to classify important data elements are listed in Table 4.[19] Standard terminologies and suggestions for minimal data sets specific to pregnancy registries are provided in Chapter 21.

Table 4. Standard Terminologies

Standard	Acronym	Description and Web site	Developer
Billing related			
Current Procedural Terminology	CPT®	Medical service and procedure codes commonly used in public and private health insurance plans and claims processing. Web site: http://www.ama-assn.org/ama/pub/category/3113.html	American Medical Association
International Classification of Diseases	ICD, ICD-O, ICECI, ICF, ICPC	International standard for classifying diseases and other health problems recorded on health and vital records. ICD-9-CM, a modified version of the ICD-9 standard, is used for billing and claims data in the United States, which will transition to ICD-10-CM in 2014. The ICD is also used to code and classify mortality data from death certificates in the United States. ICD adaptations include ICD-O (oncology), ICECI (External Causes of Injury), ICF (Functioning, Disability and Health), and ICPC-2 (Primary Care, Second Edition). Web site: http://www.who.int/classifications/icd/en	World Health Organization
Clinical			
Systemized Nomenclature of Medicine	SNOMED CT	Clinical health care terminology that maps clinical concepts with standard descriptive terms. Formerly SNOMED RT and SNOP. Web site: http://www.ihtsdo.org/snomed-ct	International Health Terminology Standards Development Organization
Unified Medical Language System	UMLS	Database of 100 medical terminologies with concept mapping tools. Web site: http://www.nlm.nih.gov/research/umls/	National Library of Medicine

Standard	Acronym	Description and Web site	Developer
Classification of Interventions and Procedures	OPCS-4	Code for operations, surgical procedures, and interventions. Mandatory for use in National Health Service (England). Web site: http://www.datadictionary.nhs.uk/web_site_content/supporting_information/clinical_coding/opcs_classification_of_interventions_and_procedures.asp	Office of Population, Censuses, and Surveys
Diagnostic and Statistical Manual	DSM	The standard classification of mental disorders used in the United States by a wide range of health and mental health professionals. The version currently in use is the DSM-IV. Web site: http://www.psych.org/MainMenu/Research/DSMIV.aspx	American Psychiatric Association
Drugs			
Medical Dictionary for Regulatory Activities	MedDRA	Terminology covering all phases of drug development, excluding animal toxicology. Also covers health effects and malfunctions of devices. Replaced COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms). Web site: http://www.meddramsso.com	International Conference on Harmonisation (ICH)
VA National Drug File Reference Terminology	NDF-RT	Extension of the VA National Drug File; used for modeling drug characteristics, including ingredients, chemical structure, dose form, physiologic effect, mechanism of action, pharmacokinetics, and related diseases. Web site not available.	U.S. Department of Veterans Affairs
National Drug Code	NDC	Unique 3-segment number used as the universal identifier for human drugs. Web site: http://www.fda.gov/cder/ndc/	U.S. Food and Drug Administration
RxNorm	RxNorm	Standardized nomenclature for clinical drugs. The name of a drug combines its ingredients, strengths, and/or form. Links to many of the drug vocabularies commonly used in pharmacy management and drug interaction software. Web site: http://www.nlm.nih.gov/research/umls/rxnorm/	National Library of Medicine
World Health Organization Drug Dictionary	WHODRUG	International drug dictionary. Web site: http://www.who-umc.org/DynPage.aspx?id=98105&mn1=7347&mn2=7252&mn3=7254&mn4=7338	World Health Organization
Lab specific			
Logical Observation Identifiers Names and Codes	LOINC®	Concept-based terminology for lab orders and results. Web site: http://www.regenstrief.org/loinc/	Regenstrief Institute for Health Care
Other			
HUGO Gene Nomenclature Committee	HGNC	Recognized standard for human gene nomenclature. Web site: http://www.genenames.org/	Human Genome Organization
Dietary Reference Intakes	DRIs	Nutrient reference values developed by the Institute of Medicine to provide the scientific basis for the development of food guidelines in Canada and the United States. Web site: http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables	Institute of Medicine Food and Nutrition Board

Standard	Acronym	Description and Web site	Developer
Substance Registry Services	SRS	The central system for standards identification of, and information about, all substances tracked or regulated by the Environmental Protection Agency. Web site: http://iaspub.epa.gov/sor_internet/registry/substreg/home/overview/home.do	Environmental Protection Agency

In addition to these standard terminologies, there are numerous useful commercial code listings that target specific needs, such as proficiency in checking for drug interactions or compatibility with widely used electronic medical record systems. Mappings between many of these element lists are also increasingly available. For example, SNOMED CT® (Systemized Nomenclature of Medicine Clinical Terminology) can currently be mapped to ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification), and mapping between other standards is planned or underway.[20]

After investigating clinical data standards, registry planners may find that there are no useful standards or established datasets for the registry, or that these standards comprise only a small portion of the dataset. In these cases, the registry will need to define and select data elements with the guidance of its project team, which may include an advisory board.

When selecting data elements, it is often helpful to gather input from statisticians, epidemiologists, psychometricians, and experts in health outcomes assessment who will be analyzing the data, as they may notice potential analysis issues that need to be considered at the time of data element selection. Data elements may also be selected based on performance or quality measures in a clinical area. (See Case Examples 6 and 50.)

When beginning the process of defining and selecting data elements, it can be useful to start by considering the registry design. Since many registries are longitudinal, sites often collect data at multiple visits. In these cases, it is necessary to determine which data elements can be collected once and which data elements should be collected at every visit. Data elements that can be collected once are often collected at the baseline visit.

In other cases, the registry may be collecting data at an event level, so all of the data elements will be collected during the course of the event rather than in separate visits. In considering when to collect a data element, it is also important to determine the most appropriate order of data collection. Data elements that are related to each other in time (e.g., dietary information and a fasting blood sample for glucose or lipids) should be collected in the same visit rather than in different visit case report forms.

International clinician and patient participation may be required to meet certain registry data objectives. In such situations, it is desirable to consider the international participation when selecting data elements, especially if it will be necessary to collect and compare data from individual countries. Examination and laboratory test results or units may differ among countries, and standardization of data elements may become necessary at the data-entry level. Data elements relating to cost-effectiveness studies may be particularly challenging, since there is substantial variation among countries in health care delivery systems and practice patterns, as well as in the cost of medical resources that are used as "inputs."

Alternatively, if capture of internationally standardized data elements is not desirable or cannot be achieved, registry stakeholders should consider provisions to capture data elements according to local

standards. Later, separate data conversions and merging outside the database for uniform reporting or comparison of data elements captured in multiple countries can be evaluated and performed as needed if the study design ensures that all data necessary for such conversions have been collected.

Table 5 provides examples of possible baseline data elements. The actual baseline data elements selected for a specific registry will vary depending on the design, nature, and goals of the registry. Examples listed include patient identifiers (e.g., for linkage to other databases), contact information (e.g., for followup), and residence location of enrollee (e.g., for geographic comparisons). Other administrative data elements that may be collected include the source of enrollment, enrollee sociodemographic characteristics, and information on provider locations.

Table 5. Examples of Possible Baseline Data Elements

Enrollee contact information	• Enrollee contact information for registries with direct-to-enrollee contact • Another individual who can be reached for followup (address, telephone, email)
Enrollment data elements	• Patient identifiers (e.g., name [last, first, middle initial], date of birth, place of birth, Social Security Number) • Permission/consent • Source of enrollment (e.g., provider, institution, phone number, address, contact information) • Enrollment criteria • Sociodemographic characteristics, including race, gender, age or date of birth • Education and/or economic status, insurance, etc. • Preferred language • Place of birth • Location of residence at enrollment • Source of information • Country, State, city, country, ZIP Code of residence

Depending on the purpose of a registry, other sets of data elements may be required. Table 6 provides examples of possible additional data elements; again, the data elements selected for a specific registry will vary and should be driven by the design and purpose of the registry. In addition, data elements that may be needed for specific types of registries are outlined below.

Table 6. Examples of Possible Additional Enrollee, Provider, and Environmental Data Elements

Pre-enrollment medical history	
Medical History	• Morbidities/conditions • Onset/duration • Severity • Treatment history • Medications • Adherence • Health care resource utilization • Diagnostic tests and results • Procedures and outcomes • Emergency room visits, hospitalizations (including length of stay), long-term care, or stays in skilled nursing facilities

Pre-enrollment medical history	
Medical History (cont.)	• Genetic information • Comorbidities • Development (pediatric/adolescent)
Environmental Exposures	• Places of residence
Patient Characteristics	• Functional status (including ability to perform tasks related to daily living), quality of life, symptoms • Health behaviors (alcohol, tobacco use, physical activity, diet) • Social history • Marital status • Family history • Work history • Employment, industry, job category • Social support networks • Economic status, income, living situation • Sexual history • Foreign travel, citizenship • Legal characteristics (e.g., incarceration, legal status) • Reproductive history • Health literacy • Individual understanding of medical conditions and the risks and benefits of interventions • Social environment (e.g., community services) • Enrollment in clinical trials (if patients enrolled in clinical trials are eligible for the registry)
Provider/system characteristics	• Geographical coverage • Access barriers • Quality improvement programs • Disease management, case management • Compliance programs • Information technology use (e.g., computerized physician order entry, e-prescribing, electronic medical records)
Financial/economic information	• Disability, work attendance (days lost from work), or absenteeism/presenteeism • Out-of-pocket costs • Health care utilization behavior, including outpatient visits, hospitalizations (and length of stay), and visits to the emergency room or urgent care • Patients' assessments of the degree to which they avoid health care because of its costs • Patients' reports of insurance coverage to assist/cover the costs of outpatient medications • Destination when discharged from a hospitalization (home, skilled nursing facility, long-term care, etc.) • Medical costs, often derived from data clinician office visits, hospitalizations (especially length of stay), and/or procedures
Follow-up	
Key primary outcomes	• Safety: adverse events (see Chapter 12) • Quality measurement/improvement: key selected measures at appropriate intervals •

Follow-up	
Key primary outcomes (cont.)	• Effectiveness and value: intermediate and endpoint outcomes; health case resource use and hospitalizations, diagnostic tests and results. Particularly important are outcomes meaningful to patients, including survival, symptoms, function, and patient-reported outcomes, such as health-related quality-of-life measures • Natural history: progression of disease severity; use of health care services; diagnostic tests, procedures, and results; quality of life; mortality; cause/date of death
Key secondary outcomes	• Economic status • Social functioning
Other potentially important information	• Changes in medical status • Changes in patient characteristics • Changes in provider characteristics • Changes in financial status • Residence • Changes to, additions to, or discontinuation of exposures (medications, environment, behaviors, procedures) • Changes in health insurance coverage • Sources of care (e.g., where hospitalized) • Changes in individual attitudes, behaviors

- For registries examining questions of safety for drugs, vaccines, procedures, or devices, key information includes history of the exposure and data elements that will permit analysis of potential confounding factors that may affect observed outcomes, such as enrollee characteristics (e.g., comorbidities, concomitant therapies, socioeconomic status, ethnicity, environmental and social factors) and provider characteristics. For drug exposures, data on use (start and stop dates), as well as data providing continuing evidence that the drug was actually used (data on medication persistence and/or adherence), may be important. In some instances, it is also useful to record reasons for discontinuation and whether pills were split or shared with others. Refer to Chapter 19 for more information on using registries for product safety assessments. For registries designed to study devices, unique device identifier (UDI) information may be collected. See Chapter 23 for more information on issues specific to medical devices.
- For registries examining questions of effectiveness and cost-effectiveness, key information includes the history of exposure and data elements that will permit analysis of potential confounding factors that may affect observed outcomes. It may be particularly useful to collect information to assess confounding by indication, such as the reason for prescribing a medication. In addition to the data elements mentioned above for safety, data elements may include individual behaviors and provider and/or system characteristics. For assessment of cost-effectiveness, information may be recorded on the financial and economic burden of illness, such as office visits, visits to urgent care or the emergency room, and hospitalizations, including length of stay. Information on indirect or productivity costs (such as absenteeism and disability) may also be collected. For some studies, a quality-of-life instrument that can be analyzed to provide quality-adjusted life years (QALYs) or similar comparative data across conditions may be useful.
- For registries assessing quality of care and quality improvement, data that categorize and possibly differentiate among the services provided (e.g., equipment, training, or experience level of providers, type of health care system) may be sought, as well as information that identifies individual patients as potential candidates for the treatment (Chapter 22). In addition, patient-reported outcomes are valuable to assess the patients' perception of quality of care (Chapter 5).

- For registries examining the natural history of a condition, the selection of data elements would be similar to those of effectiveness registries.

If one goal of a registry is to identify patient subsets that are at higher risk for particular outcomes, more detailed information on patient and provider characteristics should be collected, and a higher sample size also may be required. This information may be important in registries that look at the usage of a procedure or treatment. Quality improvement registries also use this information to understand how improvement differs across many types of institutions.

Another question that may arise during data element selection relates to endpoint adjudication. Some significant endpoints may either be difficult to confirm without review of the medical record (e.g., stroke) or may not be specific to a single disease and therefore difficult to attribute without such review (e.g., mortality). While clinical trials commonly use an adjudication process for such endpoints to better assess the endpoint or the most likely cause, this is much less common in registries. The use of adjudication for endpoints will depend on the purpose of the registry.

3.1. Patient Identifiers

When selecting patient identifiers, there are a variety of options to use (e.g., the patient's name, date of birth, or some combination thereof) that are subject to legal and security considerations. When the planned analyses require linkage to other data (such as medical records), more specific patient information may be needed, depending on the planned method of linkage (e.g. probabilistic or deterministic). (For more information on linkage considerations, see Chapter 16.) In selecting patient identifiers, some thought should be given to the possibility that patient identifiers may change during the course of the registry. For example, patients may change their name during the course of the registry following marriage/divorce, or patients may move or change their telephone number. Patient identifiers can also be inaccurate because of intentional falsification by the patient (e.g., for privacy reasons in a sexually transmitted disease registry), unintentional misreporting by the patient or a parent (e.g., wrong date of birth), or typographical errors by clerical staff. In these cases, having more than one patient identifier for linking patient records can be invaluable. In addition, identifier needs will differ based on the registry goals. For example, a registry that tracks children will need identifiers related to the parents, and registries that are likely to include twins (e.g., immunization registries) should plan for the duplication of birth dates and other identifiers. In selecting patient identifiers for use in a registry, registry planners will need to determine what data are necessary for their purpose and plan for potential inaccurate and changing data.

Generally, patient identifiers can simplify the process of identifying and tracking patients for followup. Patient identifiers also allow for the possibility of identifying patients who are lost to followup due to death (i.e., through the National Death Index) and linking to birth certificates for studies in children. In addition, unique patient identifiers allow for analysis to remove duplicate patients.

When considering the advantages of patient identifiers, it is important to take into account the potential challenges that collecting patient identifiers can present and the privacy and security concerns associated with the collection and use of patient identifiers. Obtaining consent for the use of patient-identifiable information can be an obstacle to enrollment, as it can lead to the refusal of patients to participate. Chapter 7 contains more information on the ethical and legal considerations of using patient identifiers.

In addition to the data points related to primary and secondary outcomes, it is important to plan for patients who will leave the registry. While the intention of a registry is generally for all patients to remain in the study until planned followup is completed, planning for patients to leave the study before completion of full followup may reduce analysis problems. By designing a final study visit form, registry planners can more clearly document when losses to followup occurred and possibly collect important information about why patients left the study. Not all registries will need a study discontinuation form, as some studies collect data on the patient only once and do not include followup information (e.g., in-hospital procedure registries).

3.2. Data Definitions

Creating explicit data definitions for each variable to be collected is essential to the process of selecting data elements. This is important to ensure internal validity of the proposed study so that all participants in data collection are acquiring the requisite information in the same reproducible way. (See Chapter 11.) The data definitions should include the ranges and acceptable values for each individual data element, as well as the potential interplay of different data elements. For example, logic checks for the validity of data capture may be created for data elements that should be mutually exclusive.

When deciding on data definitions, it is important to determine which data elements are required and which elements may be optional. This is particularly true in cases where the registry may collect a few additional "nice to know" data elements. It will differ depending on whether the registry is using existing medical record documentation to obtain a particular data element or whether the clinician is being asked directly. For example, the New York Heart Association Functional Class for heart failure is an important staging element but is often not documented.[21] However, if clinicians are asked to provide the data point prospectively, they can readily do so. Consideration should also be given to accounting for missing or unknown data. In some cases, a data element may be unknown or not documented for a particular patient, and followup with the patient to answer the question may not be possible. Including an option on the form for "not documented" or "unknown" will allow the person completing the case report form to provide a response to each question rather than leaving it blank. Depending on the analysis plans for the registry, the distinction between undocumented data and missing data may be important.

3.3. Patient-Reported Outcomes

When collecting data for patient outcomes analysis, it is important to use patient-reported outcomes (PROs) that are valid, reliable, responsive, interpretable, and translatable. PROs reflect the patients' perceptions of their status and their perspective on health and disease. PROs have become an increasingly important avenue of investigation, particularly in light of the 2001 Institute of Medicine report calling for a more patient-centered health care system.[22] The FDA also noted the importance of PRO data in understanding certain treatment effects in its 2009 guidance document.[23] The use of PROs in registries is discussed in more detail in Chapter 5.

When using an instrument to gather data on PROs, it is important both to collect the individual question responses and to calculate the summary or composite score. The summary score, which may be for the entire instrument or for individual domains, is ultimately used to report results. However, if the registry collects only the summary score, it will not be possible to examine how the patients scored on different components of the instrument during the registry analysis phase.

4. Registry Data Map

Once data elements have been selected, a data map should be created. The data map identifies all sources of data (Chapter 6) and explains how the sources of data will be integrated. Data maps are useful to defend the validity and/or reliability of the data, and they are typically an integral part of the data management plan (Chapter 11.2.5.).

5. Pilot Testing

After the data elements have been selected and the data map created, it is important to pilot test the data collection tools to determine the time needed to complete the form and the resulting subject/abstractor burden. For example, through pilot testing, registry planners might determine that it is wise to collect certain data elements that are either highly burdensome or only "nice to know" in only a subset of participating sites (nested registry) that agree to the more intensive data collection, so as not to endanger participation in the registry as a whole. Pilot testing should also help to identify the missing data rate and any validity issues with the data collection system.

The burden of form collection is a major factor determining a registry's success or failure, with major implications for the cost of participation and for the overall acceptance of the registry by hospitals and health care personnel. Moreover, knowing the anticipated time needed for patient recruitment/enrollment will allow better communication to potential sites regarding the scope and magnitude of commitment required to participate in the study. Registries that obtain information directly from patients include the additional issue of participant burden, with the potential for participant fatigue, leading to failure to answer all items in the registry. Highly burdensome questions can be collected in a prespecified subset of subjects. The purpose of these added questions should be carefully considered when determining the subset so that useful and accurate conclusions can be achieved.

Pilot testing the registry also allows the opportunity to identify issues and make refinements in the registry-specific data collection tools, including alterations in the format or order of data elements and clarification of item definitions. Alterations to validated PRO measures are generally not advised unless they are revalidated. Validated PRO measures that are not used in the validated format may be perceived as invalid or unreliable.

Piloting may also uncover problems in registry logistics, such as the ability to accurately or comprehensively identify subjects for inclusion. A fundamental aspect of pilot testing is evaluation of the accuracy and completeness of registry questions and the comprehensiveness of both instructional materials and training in addressing these potential issues. Gaps in clarity concerning questions can result in missing or misclassified data, which in turn may cause bias and result in inaccurate or misleading conclusions. For example, time points, such as time to radiologic interpretation of imaging test, may be difficult to obtain retrospectively and, if they do exist in the chart, may not be consistently documented. An example is time to radiologic interpretation. Without additional instruction, some hospitals may indicate the time the image was read by the radiologist and others may use the time when the interpretation was recorded in the chart. The two time points can have significant variation, depending on the documentation practices of the institution.

Pilot testing ranges in practice from ad hoc assessments of the face validity of instruments and materials in clinical sites, to trial runs of the registry in small numbers of sites, to highly structured evaluations of

inter-rater agreement. The level of pilot testing is determined by multiple factors. Accuracy of data entry is a key criterion to evaluate during the pilot phase of the registry. When a "gold standard" exists, the level of agreement with a reference standard (construct validity) may be measured.[24] Data collected by seasoned abstractors or auditors following strict operational criteria can serve as the gold standard by which to judge accuracy of abstraction for chart-based registries.[25]

In instances where no reference standard is available, reproducibility of responses to registry elements by abstractors (inter-rater reliability) or test-retest agreement of subject responses may be assessed.[26] Reliability and/or validity of a data element should be tested in the pilot phase whenever the element is collected in new populations or for new applications. Similar mechanisms to those used during the pilot phase can be used during data quality assurance (Chapter 11.3). A kappa statistic measure of how much the level of agreement between two or more observers exceeds the amount of agreement expected by chance alone is the most common method for measuring reliability of categorical and ordinal data. The intraclass correlation coefficient, or inter-rater reliability coefficient, provides information on the degree of agreement for continuous data. It is a proportion that ranges from zero to one. Item-specific agreement represents the highest standard for registries; it has been employed in cancer registries and to assess the quality of data in statewide stroke registries. Other methods, such as the Bland and Altman method,[35] may also be chosen, depending upon the type of data and registry purpose.

6. Summary

The selection of data elements requires balancing such factors as their importance for the integrity of the registry and for the analysis of primary outcomes, their reliability, their contribution to the overall burden for respondents, and the incremental costs associated with their collection. Data elements should be selected with consideration for established clinical data standards, common data definitions, and whether patient identifiers will be used. It is also important to determine which elements are absolutely necessary and which are desirable but not essential. Once data elements have been selected, a data map should be created, and the data collection tools should be pilot tested. Overall, the choice of data elements should be guided by parsimony, validity, and a focus on achieving the registry's purpose.

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Case Examples for Chapter 4

Case Example 5. Selecting Data Elements for a Registry

Description	The Dosing and Outcomes Study of Erythropoiesis-stimulating Therapies (DOSE) Registry was designed to understand anemia management patterns and clinical, economic, and patient-reported outcomes in oncology patients treated in outpatient oncology practice settings across the United States. The prospective design of the DOSE Registry enabled data capture from oncology patients treated with erythropoiesis- stimulating therapies.
Sponsor	Centocor Ortho Biotech Services, LLC
Year Started	2003
Year Ended	2009
No. of Sites	71
No. of Patients	2,354

Challenge

Epoetin alfa was approved for patients with chemotherapy-induced anemia in 1994. In 2002, the U.S. Food and Drug Administration approved a second erythropoiesis-stimulating therapy (EST), darbepoetin alfa, for a similar indication. While multiple clinical trials described outcomes following intervention with ESTs, little information was available on real-world practice patterns and outcomes in oncology patients. The registry team determined that a prospective observational effectiveness study in this therapeutic area was needed to gain this information. The three key challenges were to make the study representative of real-world practices and settings (e.g., hospital-based clinics, community oncology clinics); to collect data elements that were straightforward so as to minimize potential data collection errors; and to collect sufficient data to study effectiveness, while ensuring that the data collection remained feasible and time efficient for outpatient oncology clinics.

Proposed Solution

The registry team began selecting data elements by completing a thorough literature review. Because this would be one of the first prospective observational studies in this therapeutic area, the team wanted to ensure that study results could be presented to health care professionals and decisionmakers in a manner consistent with clinical trials, of which there were many. The team also intended to make the data reports from this study comparable with clinical trial reports. To meet these objectives, data elements (e.g., baseline demographics, dosing patterns, hemoglobin levels) similar to those in clinical trials were selected whenever possible, based on a thorough literature review.

For the patient-reported outcomes component of the registry, the team incorporated standard validated instruments. This decision allowed the team to avoid developing and validating new instruments and supported consistency with clinical trial literature, as many trials had incorporated these instruments. To capture patient-reported data, the team selected two instruments, the Functional

Assessment of Cancer Therapy–Anemia (FACT-An) and the Linear Analog Scale Assessment (LASA) tool. The FACT-An tool, developed from the FACT-General scale, had been designed and validated to measure the impact of anemia in cancer patients. The LASA enables patients to report their energy level, activity level, and overall quality of life on a scale of 0 to 100. Both tools are commonly used to gather patient-reported outcomes data for cancer patients.

Following the literature review, an advisory board was convened to discuss the registry objectives, data elements, and study execution. The advisory board included representatives from the medical and nursing professions. The multidisciplinary board provided insights into both the practical and clinical aspects of the registry procedures and data elements. Throughout the process, the registry team remained focused on both the overall registry objectives and user-friendly data collection. In particular, the team worked to make each question clear and unambiguous in order to minimize confusion and enable a variety of site personnel, as well as the patients, to complete the registry data collection.

Results

The registry was launched in 2003 as one of the first prospective observational effectiveness studies in this therapeutic area. Seventy-one sites and 2,354 patients enrolled in the study. The sites participating in the registry represented a wide geographic distribution and a mixture of outpatient practice settings.

Key Point

Use of common data elements, guided by a literature review, and validated patient-reported outcomes instruments enhanced data generalizability and comparability with clinical trial data. A multidisciplinary advisory board also helped to ensure collection of key data elements in an appropriate manner from both a clinical and practical standpoint.

For More Information

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Case Example 6. Understanding the Needs and Goals of Registry Participants

Description	The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) studied the health status of patients for one year after discharge for a myocardial infarction. The registry focused on developing a rich understanding of the patients' symptoms, functional status, and quality of life by collecting extensive baseline data in the hospital and completing followup interviews at 1, 6, and 12 months.

Sponsor	CV Therapeutics and CV Outcomes
Year Started	2003
Year Ended	2004
No. of Sites	19
No. of Patients	2,498

Challenge

With the significant advances in myocardial infarction (MI) care over the past 20 years, many studies have documented the improved mortality and morbidity associated with these new treatments. These studies typically have focused on in-hospital care, with little to no followup component. As a result, information on the transition from inpatient to outpatient care was lacking, as were data on health status outcomes.

PREMIER was designed to address these gaps by collecting detailed information on MI patients during the hospital stay and through followup telephone interviews conducted at 1, 6, and 12 months. The goal of the registry was to provide a rich understanding of patients' health status (their symptoms, function, and quality of life) 1 year after an acute MI. The registry also proposed to quantify the prevalence, determinants, and consequences of patient and clinical factors in order to understand how the structures and processes of MI care affect patients' health status.

To develop the registry dataset, the team began by clearly defining the phases of care and recovery and identifying the clinical characteristics that were important in each of these phases. These included patient characteristics upon hospital arrival, details on inpatient care, and details on outpatient care. The team felt that information on each of these phases was necessary, since the variability of any outcome over 1 year may be explained by patient, inpatient treatment, or outpatient factors. Health status also includes many determinants beyond the clinical status of disease, such as access to care, socioeconomic status, and social support; the registry needed to collect these additional data in order to fully understand the health status outcomes.

Proposed Solution

While registries often try to include as many eligible patients and sites as possible by reducing the burden of data entry, this registry took an alternative approach. The team designed a dataset that included more than 650 baseline data elements and more than 200 followup interview-assessed data elements. Instead of allowing retrospective chart abstraction, the registry required hospitals to complete a five-page patient interview while the patient was in the hospital. The registry demanded significant resources from the participating sites. For each patient, the registry required about 4 hours of time, with 15 minutes for screening, 2 hours for chart abstraction, 45 minutes for interviews, 45 minutes for data entry, and 15 minutes of a cardiologist's time to interpret the electrocardiograms and angiograms. A detailed, prespecified sampling plan was developed by each site and approved by the data coordinating center to ensure that the patients enrolled at each center were representative of all of the patients seen at that site.

The registry team developed this extremely detailed dataset and data collection process through extensive consultations with the registry participants. The coordinators and steering committees reviewed the dataset multiple times, with some sites giving extensive feedback. Throughout the development process, there was an ongoing dialog among the registry designers, the steering committee, and the registry sites.

The registry team also used standard definitions and established instruments whenever possible to enable the registry data to be cross-referenced to other studies and to minimize the training burden. The team used the American College of Cardiology Data Standards for Acute Coronary Syndromes for data definitions of any overlapping fields. To measure other areas of the patient experience, the team used the Patient Health Questionnaire to examine depression, the ENRICHD Social Support Inventory to measure social support, the Short Form-12 to quantify overall mental and physical health, and the Seattle Angina Questionnaire (SAQ) to understand the patients' perspective on how coronary disease affects their life.

Results

The data collection burden posed some challenges. Two of the 19 sites dropped out of the registry soon after it began. Two other sites fell behind on their chart abstractions. Turnover of personnel and multiple commitments at participating sites also delayed the study.

Despite these challenges, the registry experienced very little loss of enthusiasm or loss of sites once it was up and running. The remaining 17 sites completed the registry and collected data on nearly 2,500 patients. In return for this data collection, sites enjoyed the academic productivity and collaborative nature of the study. The data coordinating center created a Web site that offered private groups for the principal investigators, so that each investigator had access to all of the abstract ideas and all of the research that was being done. This structure provided nurturing and support for the investigators, and they viewed the registry as a way to engage themselves and their institution in research with a prominent, highly respected team.

On the patient side, the registry met followup goals. More than 85 percent of participants provided 12-month followup information. The registry team attributed this followup rate to the strong rapport that the interviewers developed with the patients during the course of the followup period.

Key Point

This example illustrates that there is no maximum or minimum number of data elements for a successful registry. Instead, a registry can best achieve its goals by ensuring that sufficient information is collected to achieve the purpose of the registry while remaining feasible for the participants. An open, ongoing dialog with the participants or a subgroup of participants can help determine what is feasible for a particular registry and to ensure that the registry will retain the participants for the life of the study.

For More Information

Spertus JA, Peterson E, Rumsfeld JS. et al. The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER)–evaluating the impact of myocardial infarction on patient outcomes. Am Heart J. 2006;151(3):589–97.

Chapter 5. Use of Patient-Reported Outcomes in Registries

1. Introduction

As the medical system refocuses on delivering patient-centered care, the importance of measuring and reporting those aspects of health and well-being that are best described by patients themselves, whether related to disease, treatment, or both is increasingly recognized.[1-4] Discrepancies exist between patient and clinician estimates of both the prevalence and severity of patients' symptoms as well as functional impairments, highlighting the importance of direct patient reporting.3,[5-9] A patient reported outcome (PRO) is defined as a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.[10] (See Table 7.) PROs are a subgroup of patient outcomes, which are more general and reflect any outcome related to a patient, whether reported by the patient or described by a third party (e.g., imaging, laboratory evaluation, clinician assessment).

Over the past 20 years, an expanding body of literature has demonstrated that PROs are associated with traditional outcomes, such as overall survival[11-16] and tumor response.[17] PROs themselves are increasingly recognized as valid outcomes (e.g., quality of life, pain, breathlessness, physical functioning).[18-27] Systematic collection of PROs in clinical trials, patient registries, and usual clinical care is feasible and efficient.[28-32] PROs are more reflective of underlying health status than physician reporting[33] and facilitate discussion of important symptoms and quality of life (QoL) with clinicians.[34] Additionally, they have been shown to serve as supporting documentation,[29] improve symptom management,[35] and potentially impact clinical decisionmaking,[30,36] all of which are viewed favorably.[30] As a matter of terminology, the term "health-related quality of life" (HRQoL) has emerged as the preferential choice in recent literature, and there are cogent arguments surrounding its use. However, the more general "QoL" reflects the fact that health status affects numerous aspects of daily life and influences overall QoL. Thus, further discussions in this chapter will consistently use the term QoL.

While widespread adoption of PROs as a key component in clinical research has not occurred, there is increasing recognition of their role in complementing traditional clinical and administrative data. To this end, the importance of incorporating PROs into clinical research has been highlighted by a number of national policymaking organizations.2,[37] Recently, the United States Food and Drug Administration (FDA) identified PROs as the regulatory standard for supporting subjective endpoints, like symptoms, in drug approval and labeling, and their updated guidance distributed in December 2009 provides clear instructions on PRO measurement in drug development trials.[10] While the purposes of PROs in registry studies are not for supporting labeling claims, the guidance provided by the FDA has helped refine the definition of PROs and expand the sphere of interest surrounding their use. Most importantly, the FDA guidance document has established a benchmark, albeit a high one, for PRO data and has been the focus of much recent PRO-related literature (references too numerous to list). For this reason, the standards set by the FDA are heavily referenced in the following discussion.

Presently, there are no evidence-based guidelines for inclusion of PROs in registries, leading to substantial heterogeneity in capture and reporting of PROs in this setting (see, for example, the review about some large registries in rheumatoid arthritis).[38] Recent initiatives to define how PROs should be used in oncology comparative effectiveness research (CER) are instructive,[39] as they reflect current,

collaborative opinions of many different stakeholders, and may serve as a template for inclusion of PROs in registries (Table 8).

Table 7. Definitions of Commonly Encountered Terms within PRO-related Literature

Term	Definition
Ability to detect change	Evidence that a PRO instrument can identify differences in scores over time in individuals or groups who have changed with respect to the measurement concept.[10]
Clinician reported outcome (ClinRO)	Outcomes that are either observed by the physician (e.g., cure of infection and absence of lesions) or require physician interpretation (e.g., radiologic results and tumor response). In addition, ClinROs may include formal or informal scales completed by the physician using information about the patient.[40]
Concept	The specific measurement goal, or the thing that is measured by a PRO.[10]
Conceptual framework	Explicitly defines the concepts measured by the instrument in a diagram that presents a description of the relationships between items, domain (subconcepts), and concepts measured and the scores produced by a PRO instrument.[10]
Construct validity	The degree to which what was measured reflects the a priori conceptualization of what should be measured.[79]
Content validity	The extent to which the instrument actually measures the concepts of interest.[77]
Criterion validity	The extent to which the scores of PRO measure reflect the gold standard measure of the same concept.[10]
Domain	A subconcept represented by a score of an instrument that measures a larger concept comprised of multiple domains.[10]
Health-related quality of life	The subjective assessment of the impact of disease and treatment across the physical, psychological, social, and somatic domains of functioning and well-being.[41]
Instrument	A means to capture data (i.e., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instruction for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target population.[10]
Item	An individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept.[10]
Item bank	A comprehensive collection of questions (and their response options) designed to measure an underlying construct across its entire continuum.[74]
Metadata	Structured information that describes, explains, locates, or otherwise makes it easier to retrieve, use, or manage an information source.[83]
Patient-reported outcome (PRO)	A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.[10]
Proxy-reported outcome	A measurement based on a report by someone other than the patient reporting as if he or she is the patient.[10]
Quality of life	An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment.[42]
Recall period	The period of time patients are asked to consider in responding to a PRO item or question.[10]
Reliability	The ability of an instrument to yield the same result on serial administrations when no change in the concept being measured is expected.[77]
Scale	The system of numbers of verbal anchors by which a value or score is derived for an item. Examples include VAS, Likert scales, and rating scales.[10]

Term	Definition
Score	A number derived from a patient's response to items in a questionnaire. A score is computed based on a prespecified, validated scoring algorithm and is subsequently used in statistical analyses of clinical results.[10]

Table 8. Example Guidelines for PRO Incorporation into Product-Labeling Claims in Oncology [i]

Selection of Measures	
1.	Include patient-reported outcomes in all prospectively designed comparative effectiveness research and post-marketing studies in adult oncology (including registries, observational cohorts, and controlled trials).
2.	Include systematic assessment of the following 14 patient-reported symptoms ("Core" symptom set) in all CER and post-marketing clinical studies in adult oncology: anorexia, anxiety, constipation, depression, diarrhea, dyspnea, fatigue, insomnia, mucositis, nausea, pain, sensory neuropathy, rash, vomiting.
3.	Include additional patient-reported symptoms as appropriate to a specific study's population, intervention, context, objectives, and setting (in addition to the Core symptom set), and incorporate a process that allows individual patients to report unsolicited symptoms.
4.	Measure quality of life (QOL), either via a single-item or multi-item questionnaire, in all prospective CER and post-marketing clinical studies. Inclusion of a measure that enables cost-utility analysis is encouraged.
5.	Selected measures to assess symptoms or QOL should have demonstrated content validity (based on direct patient input), criterion validity, reliability, and sensitivity in the intended patient population (including assessment of the meaningfulness of specific score changes and the ability to detect change over time), as well as an appropriate recall period. Linguistic translations should be conducted in accordance with existing methodological standards.
Implementation Methods	
6.	Limit PRO data collection so that the average patient can complete the process within 20 minutes at the initial (baseline) visit and within 10 minutes at any subsequent time points.
7.	Collect PROs as frequently as necessary to meet research objectives, without overburdening patients. When using PROs to assess potential treatment benefits, collection of PROs at baseline and following treatment completion or study withdrawal as well as at selected long-term time points should be considered a minimum standard. When using PROs to assess treatment toxicities/harms or comparative tolerability, more frequent assessment is merited such as at baseline and every 1-4 weeks during active therapy as well as at selected long-term time points.
8.	Collect PROs via electronic means whenever possible.
9.	Establish measurement equivalence when mixing modes of PRO measure administration in a study (e.g., web, telephone/interactive voice response [IVRS], handheld device, and/or paper).
10.	Employ methods to minimize missing PRO data including education of local site personnel, training of patients, and real-time monitoring of adherence with backup data collection.
Data Analysis and Reporting	
11.	Include a plan for analyzing and reporting missing PRO data in the protocol.
12.	Report the proportion of patients experiencing a change from baseline demonstrated as being meaningful to patients for each PRO measure.
13.	Evaluate the cumulative distribution of responses for each PRO measure and include cumulative distribution curves in reports and publications.
14.	Include a mechanism for alerting clinical staff in real-time about symptoms of concerning severity reported by patients during study participation.
15.	Analyze and publish results of PRO analyses simultaneously with other clinical outcomes.

[i] Center for Medical Technology Policy (CMTP). Effectiveness Guidance Document: Recommendations for Incorporating Patient-Reported Outcomes into the Design of Post-Marketing Clinical Trials in Adult Oncology. May 2012. Available at: http://www.cmtpnet.org/wp-content/uploads/downloads/2012/05/PRO-EGD.pdf. Accessed August 20, 2012. Reprinted with permission. Copyright restrictions apply.

2. The Role of PROs in Registries

2.1. Relationship between PROs and CER

Comparative effectiveness research was recently defined by the Institute of Medicine as:

> "… the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."[43]

Central to this definition is that the information generated by CER should assist consumers of health care (i.e., patients) in making decisions. Of great interest to patients are factors like QoL, symptom burden, and functional status, which are best described directly by patients, thereby implicitly emphasizing the importance of PROs to CER.[44,45] The strength of this relationship is furthered by the term patient-centered outcomes research (PCOR), which has emerged after passage of the Patient Protection and Affordable Care Act that established the Patient-Centered Outcomes Research Institute (PCORI). According to PCORI:

> "Patient-centered outcomes research helps people make informed health care decisions and allows their voice to be heard in assessing the value of health care options. This research answers patient-focused questions: (1) 'Given my personal characteristics, conditions and preferences, what should I expect to happen to me?' (2) 'What are my options and what are the benefits and harms of those options?' (3) What can I do to improve the outcomes that are most important to me?' (4) 'How can the health care system improve my chances of achieving the outcomes I prefer?'"[46]

By definition, PCOR is impossible to pursue without including the patient voice and PROs are an important tool for capturing the patient voice. As PCOR is effectively a subset of CER (and will not be referred to independently from this point), PROs are therefore critical components of CER, as well. The importance of PROs in CER is highlighted by the interest in the patient experience of the multiple stakeholders who ultimately utilize results of CER.[45]

2.2. Relationship between CER and Registries

While clinical trials are generally felt to represent the gold standard of evidence to support clinical decisions, many clinical trials are conducted under conditions that limit generalizability or do not emphasize factors that are important to patients and clinicians in the course of actual practice. Clinicians and patients face challenging decisions regarding treatment choices and toxicity profiles that are unaddressed by traditional clinical trials, and these are exactly the types of questions that CER is intended to address. Registries are important tools for answering such questions. They can evaluate effects in a more "real-world" population, improving generalizability. In uncommon diseases, where traditional clinical trials are unrealistic because of small numbers, registries can help fill the information void on any number of issues, including treatment options and responses, natural history, and QoL. Registries can be designed to answer specific questions that affect clinical practice, but were unaddressed by pivotal

clinical trials. Importantly, when partnered with electronic health records (EHRs), registries can capitalize on the massive amounts of data collected as part of routine clinical care to create datasets that more realistically represent the array of inputs that clinicians and patients assimilate in almost every clinical encounter. Electronic PRO instruments that are directly incorporated into routine clinical care, and thus directly into an EHR, are potentially important sources of PRO data for registry studies. Collection and analysis of such datasets, in the form of registries, offers the opportunity to inform clinical care in ways that are meaningful to all stakeholders in the health care system.

2.3. Importance of PROs in Registries

Having established the centrality of PROs to CER and the role of registries in CER, the importance of PROs to registries is apparent. Inclusion of PROs in prospectively collected registries is almost always appropriate. PROs contribute information across the spectrum of registry purposes described in Chapter 1 including describing the natural history of disease, determining effectiveness, measuring or monitoring safety or harm, and measuring quality. As one walks down the list of nominated purposes of registries, the substantive role of PROs in registry design becomes increasingly important.

2.3.1. Describing Natural History of Disease

A requirement of registries intended to describe natural history of disease is adequate information about symptom burden and related QoL trajectories, especially in the setting of rare diseases, inherited diseases with increasing life span (e.g., cystic fibrosis, sickle cell disease), and heterogeneous diseases (e.g., chronic obstructive pulmonary disease, breast cancer). Registries can provide useful information on the expected course of health, even in the absence of treatment, which could provide useful information regarding need for and timing of treatment. Understanding how new therapies impact patient experience can also be captured under this rubric. For example, metastatic renal cell carcinoma is a relatively uncommon malignancy for which the FDA has approved six targeted therapies within the past decade. All have different toxicity profiles and different symptom alleviation profiles; insufficient information can be derived from the pivotal clinical trials to develop optimal strategies for sequencing and timing of these therapies.[47] Registries of patients receiving routine care on these different agents (i.e., "real-world" registries), especially when containing PRO data, can help inform sequencing, timing and impact of treatments, providing critical information where there is an explosion of treatment options but a dearth of comparative information.

2.3.2. Determining Effectiveness

In registries designed to determine effectiveness, PROs also figure prominently, especially considering the importance placed upon the patient experience as a meaningful outcome in the IOM's definition of CER. Beyond traditional outcome measures such as overall survival and risk reduction, QoL is a valid marker of efficacy by itself and is best captured by PRO measures. Patient-reported symptoms can be indicators of adverse consequences of therapy (e.g., toxicity monitoring), targets for meaningful intervention (e.g., symptom control intervention), and means of understanding how patient perceptions of toxicities or effectiveness impact effectiveness (e.g., through adherence behavior). Consider a prospective registry intended to support CER for the management of early stage prostate cancer. For these patients, differentiating between and comparing surgery and radiation is best achieved from patient-reported information on symptoms of radiation proctitis, sexual health, pain, and urinary function, as well as the relationship of these factors to overall QoL and patient preference.

Within the area of toxicity monitoring, PROs are likely to take a place on center stage. The National Cancer Institute has recently developed a patient-reported version of its Common Terminology Criteria for Adverse Events, PRO-CTCAE[48] for use in cancer clinical trials. Pharmacovigilance studies provide another fertile area for PRO implementation. Perhaps even more powerful are efforts to link PROs to genomic and proteomic data in order to understand the biologic basis for toxicity phenotype. Registries intended for safety monitoring offer potential for a much more robust understanding of long-term safety than typical clinical efficacy trials and when coupled with data on effectiveness may help answer difficult questions such as "Was the intervention worth it?" especially as viewed through the patient's lens.

2.3.3. Quality Measurement

Registries intended to measure quality can incorporate PROs in numerous ways and PROs can contribute to quality assessment. In some instances, established quality standards do not exist, and registries can be used to establish realistic and acceptable standards. For example, there is an impetus to initiate quality monitoring in palliative medicine programs, but the evidence base is insufficient to establish benchmarks to define quality.[49] In such a setting, registries incorporating PROs would serve an important role in establishing definitions for quality and could then be used in real-time to monitor quality. However, some quality metrics focused on the patient experience already exist. For example, in the American Society of Clinical Oncology's Quality Oncology Practice Initiative assessment and management of pain, nausea/vomiting and dyspnea are core metrics; this requires both PRO assessment and response to findings.[50,51]

2.4. PROs in Prospective Registries versus Retrospective Studies

Having established the role for PROs across a spectrum of registries, it is important to consider the roles of PROs in prospective registries and retrospective studies. Patients' experiences are transient and are best captured "in the moment." They cannot be recreated or recalled precisely, thus highlighting the need to routinely and systemically capture PROs for prospective registries. Further, abundant evidence demonstrates that third party assessments (most notably clinicians) do not adequately reflect patients' subjective experience with care.[7,8,28,52] For example, in patients with lung cancer receiving chemotherapy, Basch et al showed that, when compared to physician assessments, patient reports of symptoms were more reflective of daily health status, as measured by EuroQoL EQ-5D.[33] As rapid-learning healthcare systems[53-55] become standard, routine capture of longitudinal and systematic PROs will happen as part of routine care, thereby simplifying the process to prospectively capture PROs for registry support.

As opposed to prospective registries, which can be designed to collect PROs as data accrue, studies constructed by manual chart extraction or from EHR queries should not attempt to retrospectively add PRO data that was not originally collected. Additionally, researchers should not ask patients to provide recalled/recreated PROs for missing data in such studies, as this may introduce recall bias. The exact length of time over which recall bias develops is unclear, and seems to vary for different experiences.[56] For pain, single-item assessments reflecting the prior week do not seem to represent actual pain levels as well as a mean of daily pain levels collected for the same one week period.[57] Thus, asking patients to precisely recall their symptom experience associated with a clinic visit at some arbitrary point in the past is fraught with pitfalls.

2.5. Other General Considerations on Inclusion of PROs in Registries

Including PROs in registries offers numerous advantages. First, incorporation of the patient voice helps keep care and research patient-centered, acknowledging the balance and tension between traditional outcomes and PROs. Further, symptom burden, QoL, and satisfaction with care are dynamic variables that cannot be recreated accurately through retrospection; they are essentially lost if not captured "in the moment." For this reason, routine, systematic, and longitudinal collection is recommended and should be a standard of practice. The importance of longitudinal collection cannot be overstated; it allows patients to serve as their own control; that is, each patient serves as his or her own comparator over time. Changes from baseline are tracked over time and linked to other interventions, such as initiation or discontinuation of a drug, or outcomes, such as change in disease status (e.g., cancer progression, cardiac event). Serial PROs address a number of critical issues. They: (1) improve our understanding of the trajectory of individual patient's symptom burden and QoL over the course of disease (or treatment); (2) remind clinicians of the variability between patients; (3) provide information on the value that the individual patient places on their health state; and, (4) are central to the efforts of CER, pharmacovigilance studies, and quality monitoring. When routine and systematic collection of PROs is incorporated into registries, the healthcare community can improve efficiency of routine care through support of billing and clinical documentation functions.

Certainly, including PROs in registries poses challenges. Collection of PROs can generate significant amounts of data and adds another layer of complexity to already complex datasets. Clinician acceptance may lag slightly for several reasons.[58] Although the history (patient reports filtered through a clinician's lens) and physical exam are central to clinical diagnosis and decisionmaking,[59] long-standing and deeply ingrained beliefs persist that clinician assessment alone is objective and unbiased, casting doubt upon the value and validity of unfiltered, direct patient reports. Regardless, collection of PROs generates more data for clinicians to consider and incorporate into care, which could be viewed as onerous and burdensome, especially since PROs are not yet ubiquitous or the standard of care. More importantly, it is largely unclear how PROs collected within the context of clinical research should be used to inform care and change daily practice patterns. Without appropriate infrastructure for responding to critical reports, collection of PROs may pose a liability if critical data do not receive appropriate clinician attention and response. For example, significant liability could result if a patient reports a constellation of symptoms known to be strongly associated with suicidal behavior and there is inadequate clinical intervention. Further, it is possible that PROs could lead to decreased satisfaction with care if patients expect that their PROs will be reviewed and addressed, but are unmet or unacknowledged in the clinical encounter.[29]

3. What Methods Are Available to Collect PROs and Which Is Best?

Often, choice of PRO instrument and mode of administration are considered jointly, however, they need not be, as administration methods simply provide a platform for collecting and presenting information. There are two main ways of collecting PRO data – on paper and electronically.

3.1. Paper-Based Methods

Historically, PROs were collected via paper forms and were developed based on this collection method. From a practical standpoint, collection of PRO data via paper-based methods is relatively straightforward. After selecting the instrument(s) to be used (discussed further in Section 4 below), consistency is the guiding principle. Items should be presented in the same order for every collection. If the PRO measurement selected is a single-item tool, this is automatic, but if multiple instruments are employed,

presenting them in the same order is important. Patients should complete forms in a confidential space, without fear that "wandering eyes" will see responses. Once forms are completed, they should be reviewed multiple times for completeness. For those instruments completed in clinic, this review should be done by staff collecting the instruments, nurses involved in patient intake and rooming, and clinicians reviewing responses. Once forms are submitted to the research team for data entry, completeness should be reassessed. Patients who fail to complete a pre-defined percentage of questions (there is no consensus on an acceptable percentage), should receive a followup telephone inquiry to attempt to minimize missing data. Finally, data should be entered into electronic forms using double data entry or similar techniques to enhance transcription accuracy, ideally augmented with near real-time exploratory analyses to examine the believability of the data within the clinical context.[60]

Paper forms are the historical gold standard for PRO collection. For this reason, patients are inherently familiar with them. Their use is not limited by unfamiliarity or unease with new technologies, although unfamiliarity with new technology dissipates quickly and patients are increasingly familiar with technology as advances continue to disseminate. They do not require significant upfront capital investment, in terms of devices or software. There are many measurement instruments across a variety of disease states that have been extensively evaluated and are available for immediate use.

However, paper forms have many limitations. They require research personnel to sort, distribute, and collect, introducing risk for inconsistencies and a source of ongoing cost. Paper forms collected as part of routine/scheduled clinic visits are generally straightforward, but this approach systematically misses participants unwilling or unable to attend a clinic appointment. Collection between visits is logistically difficult with paper forms; delivery of the paper forms either requires that participants take paper booklets home with them or that research personnel coordinate timely delivery of booklets through the postal service. With either approach, obtaining a time/date stamp for at-home, paper-based administration remains a challenge. Relying on at-home paper booklets risks participants completing multiple days of reporting all at once (i.e., the so-called "parking lot" effect[61] in which all responses for the past month are completed immediately before a visit while sitting in the parking lot). Paper forms often include illegible or uninterpretable responses and require manual data entry, which is administratively burdensome and subject to transcription errors. Manual entry also generates a lag time in monitoring response rates, complicating the process of reducing missing data.[62] Overall, there is a threshold beyond which the continuing data collection and quality assurance costs of paper-based PROs surpass the upfront technology costs for electronic data capture, making electronic PROs the more efficient and reliable approach.

3.2. Electronic Capture Methods

With the advent of portable and more cost-effective electronic capture methods, the presence of such methods within the literature has grown. Similar to traditional paper-based collection, electronic collection begins with instrument(s) selection. Integral to the choice of instruments is the choice of platform, as not all instruments are tested across multiple platforms, nor is every instrument amenable to every platform. Electronic PRO (ePRO) capture has been demonstrated on a variety of platforms, including web-based, electronic tablets, interactive voice response system (IVRS), handheld device, and digital pen. For ePRO collection using tablet computers or handheld devices in the clinic setting, patients are provided the device at the time of check-in to clinic with pre-loaded PRO measures such that patients simply select their response to each item as it is presented. With the digital pen, patients select responses

on a specially designed paper survey, with responses electronically recorded by the pen. With IVRS, patients call a telephone number and are prompted, via an automated transcript, to select a preferred language, provide an identifier and then are guided through the PRO measure, providing verbal responses to each item. Access to web-based platforms can be provided at "confidential" computer stations in clinic waiting rooms, or in the exam room itself, as well as from any web-enabled device including home computers, handheld devices, and mobile telephones. Regardless of platform, data are transmitted to a central, secure repository immediately upon submission and can be accessed for "real-time" incorporation into routine care, if desired. Both web-based and IVRS collection platforms can extend beyond the clinic and capture PROs between visits. Factors influencing platform selection include budget and technical support, technology literacy of the registry's target population, collection logistics (in-clinic, between-visit, or combination), and the instrument(s) chosen.[622]

Electronic methods of PRO capture have been widely shown to be feasible in a variety of practice settings, disease states, and age ranges.[29,30,63] Recently developed PRO measures have either been created specifically for electronic data capture or include features to capitalize on electronic capture technologies, such as the Patient-Reported Outcomes Measurement Information System (PROMIS),[64-66] the PRO-CTCAE,[488] and the Patient Care Monitor, version 2 (PCM).[67] The PROMIS and PRO-CTCAE tools take advantage of electronic functionalities such as skip logic or computerized adaptive testing, which can reduce the number of items patients have to complete, while the PCM also fulfills clinical documentation needs for clinical review of systems and triggers for accompanying patient education.

In terms of obtaining hardware or software for these purposes, hardware often requires an upfront investment. Again, the size of the investment depends largely upon the scope and scale of the registry. Some software packages are publicly available (e.g., PROMIS Initiative items) while others are proprietary. Third party commercial vendors specializing in design and implementation of PROs offer a variety of products. The decision to involve a commercial vendor depends upon factors like the rationale for including PROs in the registry, the size of the registry and number of involved sites, local technological expertise and support, whether the data will be collected as part of routine care or just for research purposes, and the degree of psychometric analysis needed. Although registry studies are not viewed as sufficiently rigorous for product labeling, exploratory analyses of PROs from a registry may serve as the basis for a subsequent trial for labeling purposes, in which case having a sound PRO measure in the registry could simplify the trial process. In such a scenario, using a commercial vendor to ensure adequate audit trails and compliance with all FDA guidance for PROs would be prudent. Alternatively, consider a healthcare system with an extensive EHR that plans a registry to monitor the impact of a series of clinical pathways to lessen the debilitation following major abdominal surgery; they may elect to develop or modify a PRO system to be directly integrated with their EHR without involving an ePRO vendor.

Compared to paper methods, delivery of ePROs can be automated, minimizing the risk of inconsistent presentation of materials or mishandling paper forms. Electronic collection of responses provides immediate and accurate time/date stamps, and facilitates real-time monitoring of response rates and review for missing data.[62] Additionally, electronic platforms may provide a safer environment for patients to disclose sensitive concerns, such as sexual function.[68]

Not all PRO measures were developed for, or have been tested on, electronic administration platforms. The transition of paper-based measures to electronic platforms is referred to as "migration" and guidelines were recently developed to assess the equivalence of measures that have migrated from one collection mode to another.[69] In general, paper to electronic migration yields between-mode equivalence comparable to the test-retest reliability of the original mode, but this is not always the case and should be tested.[70] When incorporating a migrated PRO measure into a registry, registry developers should verify that the ePRO measure has demonstrated validity in the intended mode of administration or reasonable equivalence with the mode for which validity, reliability, and sensitivity were initially demonstrated.[39]

Although electronic capture provides substantive advantages over paper-based methods, enthusiasm must be tempered on several fronts. First, completion of electronically delivered PRO measures requires some level of comfort with and access to newer technologies, which may prove challenging in certain situations. For example, in rural areas, using web-based methods to collect PROs between visits may be impractical due to unpredictable internet access, while some geriatric populations may be uncomfortable with tablet or handheld technologies. Second, if paper-electronic equivalence has not already been verified for a migrated PRO instrument, the process of documenting equivalence can be time-consuming and expensive. Finally, electronic methods require greater up-front investment in terms of the devices and software, electronic storage (meeting appropriate security standards), training, and technical support. Depending upon the scale of the registry, these issues may render electronic methods too burdensome.

Software selection is a common question. While outside the scope of this chapter, some broad advice can be provided. First, there are many companies that offer software to collect ePROs. Publically available software is also in production (e.g., PROMIS) or being developed (e.g., ePRO CTCAE). The software solution itself is relatively simple and expensive systems are not needed, unless specific features are required (e.g. requirement to be compliant with the FDA's CFR Part 11). Software should be from a credible vendor, with available security documentation. Since patients will likely enter Protected Health Information (PHI), the system should be appropriately compliant with the Health Insurance Portability & Accountability Act (HIPAA). Avoid using survey software where HIPAA compliance and other requirements cannot be documented.

In general, patients should report few items or ideally one item per screen, the screen should be clear and move to the next item when the answer is provided, and there should not be any software delays between questions. Visually the software should present questions and response "buttons" in large enough font for easy reading by mildly visually impaired individuals. Validation code and verifications should be built into the software, as well as any required clinical triggers. It should be easily adaptable, and easily integrated into the registry workflow. Reports (e.g., for clinicians) should be visually appealing, efficient and informative. Whenever possible, software should connect into the EHR workflow, including embedding data into the EHR for clinical documentation and/or contributing to an enterprise data warehouse.

Finally, ensure that the software has been tested before full-scale implementation with the registry. Request testing documentation from the vendor, who should have completed this. Both usability and feasibility should be considered, and it should be conducted with the planned population for the registry. As elaborated on www.usability.gov, usability is not a single, one-dimensional property of the interface, but rather a synthesis of:

- Ease of learning - How fast can a user who has never seen the user interface before learn it sufficiently well to accomplish basic tasks?
- Efficiency of use - Once an experienced user has learned to use the system, how fast can they accomplish tasks?
- Memorability - If a user has used the system before, can they remember enough to use it effectively the next time or does the user have to start over again learning everything?
- Error frequency and severity - How often do users make errors while using the system? How serious are these errors, and how do users recover from these errors?
- Subjective satisfaction - How much does the user like using the system?

The degree of usability testing should match the complexity of the task. For an ePRO system, this process minimally includes documentation of respondents' ability to navigate the electronic platform, follow instructions, and answer questions, with an overall goal of demonstrating that respondents can complete the computerized assessment as intended. Generally, fewer than ten representative patients are required to verify usability. If the system is not usable, then it should be iteratively updated until it is usable.

Feasibility extends usability and establishes the practical implementation of the software system in the local setting (e.g., clinic, home, hospital). Assessment approaches are similar and the software goes through iterative updates until feasible. During this process, patients can contribute critical advice for the "help" manual and instruction sets.

Although most often associated with questionnaire development, cognitive debriefing is also appropriate for usability and feasibility assessment through verbal probing by the interviewer (e.g., "What does the instruction 'skip item' mean to you here?") and "thinking aloud" in which the interviewer asks the respondent to verbalize whatever comes to mind as they conduct a task. Incorporated in usability and feasibility testing, cognitive debriefing helps to assess whether the ePRO system influences the way respondents interpret the questions, decide on an answer, and respond. In addition, it can help to determine whether the instructions are clear or if anything is confusing.

3.3. Which Method is Best?

As with most other aspects involving PROs in registries, the choice of PRO capture method is highly dependent upon the design and purpose of the registry. Both paper-based and electronic platforms offer advantages and disadvantages, as outlined above. Ideally, when either method is shown to be valid for an instrument, both methods of PRO data collection should be available in a study. Providing an interface familiar to or preferred by particular patients or populations may reduce missing data not at random. Modes may be mixed across patients in a study (e.g., each patient selects a specific mode at baseline and continues to report via that mode throughout a study), or within patients (e.g., a patient reports by web until he becomes symptomatically ill, at which point IVRS becomes preferable). One mode may be preferred at a particular site, for example in multinational studies where IVRS or web access are heterogeneous across countries. "Real-world" registries are likely to enroll patients from a variety of settings (e.g., home, hospital, assisted living facility) and circumstances (e.g., independent, caregiver-assisted), such that flexibility in mode of administration facilitates capturing a broad mix of patients. Mixing modes is generally viewed as acceptable if a reasonable level of between-mode equivalence has been demonstrated.[39]

In general, electronic capture is preferred to paper because of its flexibility and its ability to reduce the chance that the PRO data in a registry will be missing. In contemporary research, paper methods are usually most cost effective until registries start to grow in size or number of sites. When the registry is going to be intentionally small (e.g., fewer than 100 patients), paper methods will likely suffice. When the registry is going to be large, upfront investments in electronic approaches will realize substantial downstream gains in efficiency, cost, and data quality. Regardless of the ultimate choice of administration method, clear documentation of the rationale for the choice and clear evidence of appropriate psychometric assessment is strongly recommended. Assistance with this process may arise from internal expertise (as in many academic institutions) or may rely upon input from a commercial vendor, whose involvement can range from consulting only to nearly full control of the development and implementation process.

4. Which PRO Measure Should Be Selected?

The process of choosing which PRO measure(s) to include in a registry can be challenging, largely because the plethora of available measures is overwhelming. In 2007, a PubMed search for PRO instrument development articles since 1995 resulted in more than 2000 citations.[71]

Existing PRO measures assume a variety of forms:

- general assessment scales (e.g., health-related QoL)
- disease-specific scales [e.g., chronic obstructive pulmonary disease, cancer (including scales for individual tumor types), arthritis, or psoriasis]
- symptom-specific scales (e.g., pain, breathlessness, distress)
- evaluations of functioning across a variety of domains (e.g., physical, social, emotional)
- scales assessing satisfaction with care received
- other (e.g., adherence with therapy)

Some PRO measures are extensive, with dozens of items related to a single concept (e.g., breathlessness), while others have 80 or more items reflecting many different patient-reported concerns constituting an entire clinical review of systems, and yet others are single-item instruments measuring a single construct in a single question.

Further, there is extensive literature describing the important characteristics (i.e., conceptual framework, content validity, reliability, ability to detect change) of PRO measures, but consolidating this information into practical guidance for selecting among existing PRO measures is difficult. The FDA Guidance document has outlined a standard for evaluating PRO measures for labeling claims that encompasses the salient points regarding development history, conceptual framework, and psychometric evaluation. The standards outlined by the FDA may be more stringent than is necessary for certain registry purposes, but nevertheless serve as an important and well-conceived framework for discussion and conform to accepted best practices.[28] While a comprehensive review of PRO development and psychometric evaluation is beyond the scope of this chapter, below is a concise overview of the process and concepts. For more information, several texts provide detailed descriptions.[26,27,72]

4.1. Getting Started and the Importance of Clarity

The key to successfully navigating this process is to clearly define the following aspects of the registry:

- population of interest (e.g., cancer patients receiving radiotherapy for painful bony metastases, individuals with oxygen-dependent chronic obstructive pulmonary disease, children with rhinoconjunctivitis, United States veterans with rheumatoid arthritis)
- outcomes of interest, also known as the concept (e.g., specific symptom severity, overall symptom burden, treatment-related toxicities, physical functioning, social functioning, QoL)
- intended users of the registry (e.g., clinicians, patient advocacy groups, pharmaceutical companies, insurance companies, governmental agencies)
- the purpose(s) of the registry (e.g., pharmacovigilence, establish symptom trajectories, correlate survival benefit with QoL or symptom benefit).

As with any research activity, *a priori* specific aims and hypotheses to be tested must be outlined up front, and PRO selection appropriately aligned. Registry studies, in particular, are susceptible to poorly defined outcomes; PRO instruments may be chosen because they are general in nature and capture a broad range of patient-reported concerns, meet a target goal of demonstrating that PROs are captured rather than capturing specific PRO concepts of interest. If the objectives of the registry, intended hypotheses, and outcomes of interest are clearly defined, the desired characteristics of the PRO instrument become more clearly delineated, facilitating a search of existing measurement instruments.

4.2. Potential Sources for Identifying PRO Instruments

Once these issues are clearly defined, identification of candidate PRO measures can begin in earnest. In general, the process of PRO development is time- and resource-intensive and using existing measures whenever possible is best. It is highly unlikely that any existing instrument will perfectly suit the needs of a registry study, or that a "perfect" instrument can be developed, further underscoring the importance of clearly defining the population, outcomes of interest, and purpose of the registry. Such clarity will allow more appropriate assessment of the relative strengths and weaknesses of existing PRO measures. In many cases, modifications to existing measures will improve the measure for use in a registry. These modifications can include changes in wording or order of questions, adding specific questions, or altering the method of administration. In general, such modifications require some degree of psychometric reassessment, though the degree to which instrument modification requires psychometric reassessment varies and is discussed by Snyder et al.[73]

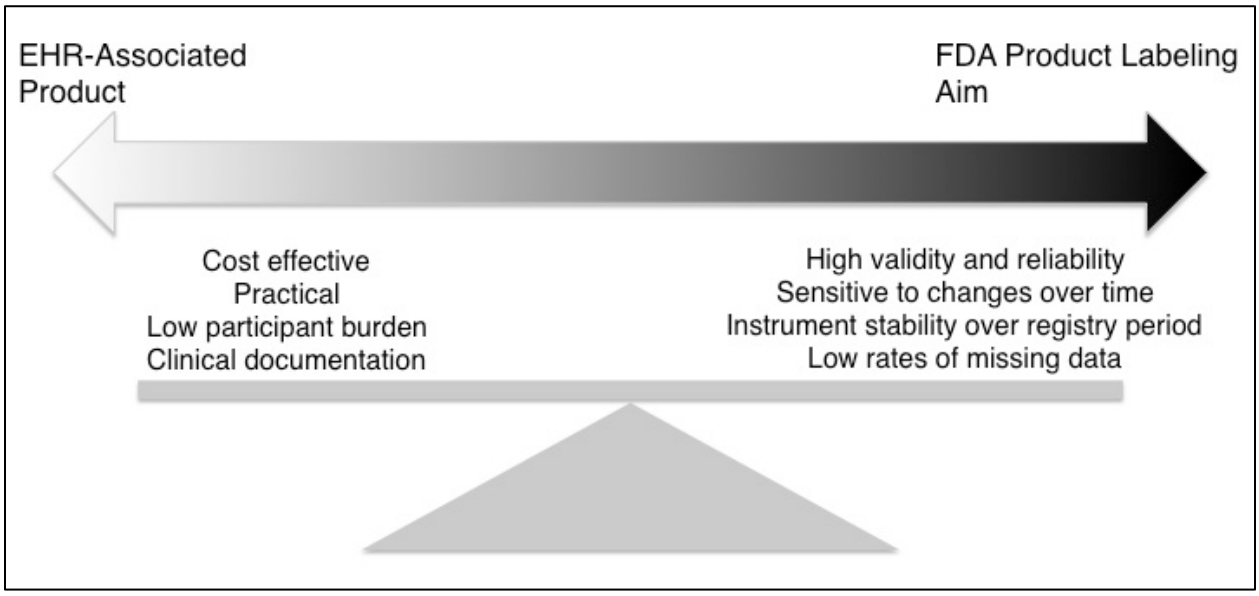
Traditional literature searches can yield results, but may be quite time-consuming. The Mapi Institute maintains the Patient-Reported Outcome and Quality of Life Instruments Database (http://www.proqolid.org), allowing users to search a large and relatively comprehensive database for PRO instruments that best address the specific needs identified. The Online Guide to Quality-of-life Assessment (http://www.olga-qol.com) is another database of existing QoL instruments. Additionally, the U.S. National Institutes of Health PROMIS Initiative (http://www.nihpromis.org) has been tasked with developing rigorously tested item banks across a broad range of domains and subdomains (functioning, disability, symptoms, distress, and role participation).[64] The PROMIS Initiative is also actively evaluating methods to achieve brevity in instruments through techniques such as computer adaptive testing. Importantly, these measures are publicly available through the PROMIS Assessment Center (http://www.assessmentcenter.net). Commercial vendors can also aid in identifying appropriate measures; as with selecting a mode for administering the PRO measure, the decision to involve a commercial vendor is multifactorial, depending on the factors described in Section 3.2 above.

Item banks represent another option for developing PRO surveys. In general, item banks contain comprehensive collections of items that pertain to a particular construct (e.g., dyspnea).[74] Item banks generally rely on item response theory (IRT), in which the unit of focus is the item, rather than the entire instrument. As such, instruments can be constructed using IRT that employ only those items which provide the most useful and relevant information, eliminating questions with little added value, without compromising psychometric qualities.[75] The PROMIS Initiative is an example of an item bank.[74] Item banks may represent the future of PRO collection, but they are currently limited by logistical issues, questions about whether IRT-based item banks represent an improvement over existing PRO instruments, concerns over regulatory acceptance, and limited data about psychometric properties of item banks in specific populations.[74] However, IRT-based item banks represent a promising approach, especially in light of the emphasis on limiting respondent burden.

4.3. Choice of the Best PRO for the Registry

Section 4.4 below describes many of the properties of PRO instruments that should be considered when choosing the appropriate instrument for each unique registry scenario. Whether to adhere closely to the conservative FDA recommendations is a frequent source of question, if not frank tension. While there is no formal avenue through which registries can support product-labeling claims, if the registry is in any way tied to trials with aspirations of product-labeling then the answer is straightforward and the FDA PRO guidance should be followed. Anchoring the FDA threshold as a "maximally conservative" (and therefore usually least practical) state, there is a continuum of scenarios and a continuum of practical allowances to the ideal state where the need for precision and reduction of bias is balanced with the need for practical solutions and the reduction of missing data (Figure 2). Figure 2 shows that the tension between psychometric desirability and logistical considerations of PRO collection in registries requires a careful balance, driven primarily by the goals of the registry. Explicitly outlining the registry objectives, population, outcomes, and intended uses as described in Section 4.1 above will help to define where the registry is on the continuum and guide decisionmaking.

Figure 2. Psychometric Properties and Logistical Considerations Exist along a Spectrum



4.4. Development History and Conceptual Framework

The PRO development history and conceptual framework are inextricably linked and are discussed in close proximity for this reason.

4.4.1. Development History

The FDA Guidance document strongly recommends transparency with respect to development history. "Development history" explicitly refers to the entire process of developing and psychometrically evaluating a patient reported outcome measure, including the conceptual framework, item development and revision history, and evidence of patient input. For newly developed PRO instruments, clearly documenting the development history is straightforward and can be integrated into the development process. Contrast this to using an existing measure, where the development history may be very difficult, if not impossible, to obtain. Ideally, the development history is well vetted in the literature, but if the history is somewhat opaque, the FDA has indicated that demonstration of content validity with specific examples, including direct patient input from the appropriate population, is an acceptable alternative. For newly developed PROs, it is imperative, from an FDA and product-labeling standpoint, that the entire development history be well documented. The cornerstone of the development history is the conceptual framework.

4.4.2. Conceptual Framework

Clear identification of the target population, purpose of the registry, and outcomes of interest greatly facilitates developing a conceptual framework. According to the FDA Guidance document, a conceptual framework "explicitly defines the concepts measured by the instrument in a diagram that presents a description of the relationships between items, domain (subconcepts), and concepts measured and the scores produced by a PRO instrument."[10] Initially, the conceptual framework arises out of expert opinion and literature review. The framework is then refined by qualitative methods of patient input, such as patient interviews and focus groups, which ensures that *a priori* hypotheses are consistent with patient experiences and descriptions. The conceptual framework will be modified iteratively.[76] For complex concepts, such as breathlessness, multiple domains affect the overall concept, so identifying appropriate domains and then assessing these is paramount to assessing the overarching concept.

4.5. Psychometric Properties

Entire texts are written on psychometrics and there is an extensive literature on psychometric properties of PRO measures. An excellent series arising from the Mayo/FDA Patient-Reported Outcomes Consensus Group focused on PRO development in advance of the anticipated FDA Guidance; it was published in a special supplement of the November/December 2007 issue of the journal *Value in Health* and provides more detailed descriptions of processes and procedures needed to implement PRO systems to meet FDA expectations.

Almost every guideline regarding utilizing PRO measures recommends selecting measures that have demonstrated content validity, criterion validity, reliability, and sensitivity (including the ability to detect change over time) in the target population.[39] It is important to note that psychometric properties are not dichotomous and instruments are not completely "valid" or "reliable." These properties are continuous variables relaying incremental information. Additionally, it is inappropriate to refer to an instrument as "validated" as this simply means it has been subjected to psychometric analysis, but conveys no information regarding the measure's performance.[77] For this reason, instruments are reflected at varying

points on our continuum in Figure 2 to demonstrate that differing states of reliability and validity may be appropriate depending upon the context of the registry and the PROs to be captured within it. The goal, ultimately, is to identify or develop instruments with acceptable psychometric properties in the population of interest.

4.5.1. Validity

From a psychometric standpoint, validity has three main forms: content, construct, and criterion validity. Content validity is the extent to which the instrument actually measures the concepts of interest. The FDA Guidance understandably places significant emphasis on content validity, consistent with other groups,[78] even stating that without adequate content validity, labeling claims cannot be supported. At face value, the importance of content validity is intuitive; it is important that an instrument assess those concepts it was designed to measure. In general, qualitative evidence, in the form of documented patient input through focus groups, is an important standard in the view of the FDA.[77] Construct validity describes the degree to which what was measured reflects the *a priori* conceptualization of what should be measured.[79] Subcomponents of construct validity are convergent and discriminant validity, which assess the degree of similarity between measures that are theoretically similar (convergent validity) or the extent to which measures that are theoretically different actually differ (discriminant validity). For example, a new measure of anxiety would be expected to have high convergent validity with the anxiety subscale of the Hospital Anxiety and Depression Scale.[80] To that end, the FDA would expect comparisons of new PRO measures with similar existing measures to support construct validity. Criterion validity describes the extent to which the scores of PRO measure reflect the gold standard measure of the same concept.[10] Criterion validity is often difficult to assess in the PRO arena because identifying gold standard measures for many PRO concepts is difficult and the FDA therefore deemphasizes criterion validity.

4.5.2. Reliability

Reliability reflects the ability of an instrument to yield the same result on serial administrations when no change in the concept being measured is expected. The reliability of an instrument is typically assessed via test-retest methods and by measuring the internal consistency.[77]

4.5.2.1. Test-Retest Reliability

Test-retest reliability describes the ability of an instrument to generate the same results in the same respondent over a period of time during which no change is reasonably expected.2,[10,77] Thus, test-retest reliability assesses the intra-individual variability. Identifying the optimal timeframe for retesting can be challenging, and may vary by disease state and target population.[77]

4.5.2.2. Internal Consistency Reliability

Internal consistency reliability reflects the degree to which items within a scale measure the same concept. It can be quantitatively assessed with Cronbach's alpha, which measures the internal consistency of an instrument. Well-established thresholds for interpreting Cronbach's alpha are available; in general, coefficient alpha greater than 0.7 is the minimum acceptable threshold for comparisons between groups.[77]

4.5.3. Ability to Detect Change

The ability of a PRO measure to detect change is intuitively important. Demonstration of this ability, according to the FDA, requires that changes in the PRO instrument parallel changes in other factors that indicate a change in the status of the concept of interest. For example, in patients receiving a new treatment for opioid-induced constipation, changes in a PRO instrument designed to assess overall bowel

health may be linked with use of certain other bowel products, such as enemas, to establish the ability to detect change. The measure must demonstrate ability to detect both improvements and losses in health status. Further, it is important to detect changes throughout the range of possible values. In registry studies, where longitudinal collection and analysis are critical, understanding the concept of minimally important change detected,[81] rather than establishing that number explicitly, may be sufficient.

4.5.4. Areas of Controversy

The emphasis placed upon content validity has generated some controversy as PRO developers attempt to improve content validity, in part by meticulously wording items and instructions to minimize variations in interpretation between patients. However, the ability to improve content validity likely is asymptotic, in that individual variability undoubtedly influences interpretation of questions in ways that cannot be accounted for, meaning that responses to an instrument capture the patient's true (and unique) perceptions. There are concerns that in the pursuit of greater content validity, other important characteristics of PRO instruments may be underdeveloped or underappreciated.[79] For example, in pursuing greater content validity, the constraints placed upon questions may actually limit patient perspective by forcing some degree of conformity, or may result in misinterpretation of results. Consider a registry of patients with advanced cancer designed to assess the impact of certain interventions upon the development of disability. Upon entering the registry, a patient rates his disability as severe because his reference point is a previously healthy state. Four months later, he rates his disability as mild, though on more open-ended questioning, notes he can simply sit on the front porch and watch his grandchildren as he knows that any other activities are unrealistic and his goal is to simply make it to the front porch. Even though the instrument measures disability from the view of the patient and would thus have adequate content validity, the interpretation regarding the merits of the intervention would be erroneous, as the patient has clearly become more disabled, but has shifted his frame of reference, a fact which is not captured by content validity. This phenomenon is commonly referred to as "response shift" and has long been recognized as a challenge in QoL research.[82] Alternatively, all measures with marginal content validity may be cast aside without consideration of other properties. Consider two new measures for the same concept tested in different studies with different methodologies, resulting in different content validities. The measure with higher content validity is likely to propagate, even if it is more flawed, simply because of methodological issues.

These arguments on content validity are not intended to undermine the standards established by the FDA, nor should they be viewed as rationale for not adhering to these standards, but are meant to prompt careful consideration of all the psychometric properties of PRO measures, especially in the context of the specific registry. Remember first principles – before anything else, it needs to make good sense, have face validity, be doable, and limit patient burden.

4.6. Non-Psychometric Considerations

Beyond identifying a PRO instrument with desirable psychometric properties, consideration must be given to the *people* that are closely tied to completing and acting upon PRO data and the tension that can exist between impacts on people and psychometric desirability.

4.6.1. Patient Factors

In designing registries and considering PROs for inclusion, it is important to consider the burden to the patient the PRO measures represent. For instance, lengthy questionnaires may result in increasing missing

data over time, as patients grow weary of serially completing such questionnaires. The capacity to answer lengthy instruments cannot be predicted *a priori* and differs between groups. At Duke Cancer Institute, patients in a variety of solid tumor clinics routinely complete 80-86 item instruments without significant fatigue or burnout;[677] median time to complete the survey is 11 minutes, reducing to <8 minutes after several visits in the clinic using the same instrument. While the FDA did not offer specific recommendations on questionnaire length, a guidance document from the Center for Medical Technology Policy recommends that, for patients with cancer, completion of PRO instruments take no more than 20 minutes at the initial visit and fewer than 10 minutes at subsequent visits.[39] Patients should be offered a private space for completing instruments, to minimize concerns regarding confidentiality, especially for sensitive questions. Instructions should be provided for every item, even if it only frames the recall period. The instrument should be delivered with adequate font size and at appropriate literacy levels. Additionally, physical assistance should be provided if needed, such as reading items aloud to patients with visual impairments. While most pilot studies of PRO instruments provide a small amount of remuneration,[29,67] these studies have demonstrated that the collection of PROs made patients feel encouraged that their clinicians were seeking additional information and felt that the ePRO instrument facilitated communication between patient and clinician.[29] Outside the pilot testing phase, it is not advisable to provide remuneration to patients for completing PRO instruments, even in the setting of a registry study. PRO responses should be shared with clinicians, as this has been shown to be an important aspect of PROs to patients.[29]

4.6.2. Clinician Factors

Even within the research setting, assessing the impact of PRO collection on routine care is important. Will the PRO results be made available immediately as part of routine care or only available to research personnel? Whether or not PRO data are shared with clinicians in real time should be explicitly addressed in the informed consent process. If data are to be made available to clinicians, are appropriate support services available to assist in managing newly identified concerns or issues? Are there mechanisms to support incorporation of PRO data into clinical care, if it will be made available, or will it be "one more thing" for which clinicians are responsible? What will be the impact of the PRO collection on workflow?

Many recent guidelines recommend providing clinician feedback of concerning patient-reported information, such as reports of new chest pain. The thresholds for triggering a clinical alert, components of the alert message, and method of delivering the notice to the clinician must be carefully considered. What are the risk management concerns? How will the clinician's response be verified? Though often mundane, these factors are important to consider in the implementation phase. Teams experienced in embedding PROs into registries and clinical workflow can provide sage advice as to how to navigate these pathways (e.g., Duke Cancer Care Research Program, http://www.cancer.duke.edu/dccrp/); clear guidelines do not exist. See further discussion in Section 4.7. below.

4.6.3. Ensuring Data Quality

Collecting quality data is an implicit necessity of any registry. Although assessing data quality can assume many forms, for the purposes of registries, there are two concepts that are critical. The first is to minimize missing data. Missing data are anathema to quality data. Missing data degrades the quality of the information, thereby decreasing its analytic potential. It is essential to anticipate missing data and to plan interventions to reduce missing data. This is especially important in registry studies where time horizons are long and the potential for missing data great. There are a number of steps that can be taken to

minimize missing data during the implementation phase of the registry. The most important step is to make sure that the PRO instrument chosen is meaningful, and the role in the registry and related work is well described, especially to patients and families. Ideally, the PRO measures should be implemented as standard of care, such that they become ubiquitous and desired, not only by patients, but also by clinicians.[54] If this occurs, missing data should decrease. Electronic data collection practically supports real-time, or near real-time, quality monitoring of information being collected in order to identify patterns of missing data, leading to development of targeted interventions to reduce missing data. Additionally, with near real-time quality analysis, backup data collection methods can—and should—be deployed. For example, a central telephone interviewer can contact individuals who did not respond to items (either individually or entire instruments) to both obtain the data and ascertain why the item was omitted. Analytic approaches must include a plan for managing the unavoidable occurrence of missing data; importantly, a "last observation carried forward" approach to handling missing data should be avoided.

The second issue related to data quality is consistency. In registries with long time horizons, it is not uncommon for measurement items, or instruments, to evolve or change entirely. Unfortunately, it is equally uncommon for notations of such changes to be embedded within the data structure, as metadata, such that future analyses can quickly and readily identify which iteration of an instrument was completed at which point in time. Metadata is essentially data about data. More precisely, it is "…structured information that describes, explains, locates, or otherwise makes it easier to retrieve, use, or manage an information source."[83] Consider a long-term registry where the primary measurement instrument undergoes an iterative update to "version 2" to reflect new knowledge in the field and is quickly implemented into the registry. Though the two versions are likely very similar, they also likely have slightly different questions (in terms of structure or order), psychometric properties, and scoring algorithms. In such a scenario, it is imperative that the version of the instrument completed at any given point in time be identified within the dataset. Further, there may be cases where the person completing the questionnaire may not always be the patient (see discussion in Section 4.6.4. below). For example, in a palliative care registry, patients are not always able to complete a PRO instrument, even with assistance. The ability of the person to complete the instrument may change over time as cognition wanes. In these settings, proxy-reports involving close family or caregivers may become the only available measures and the only available data to be incorporated into registries; therefore, it is essential to identify, via metadata, who is completing the instrument.

4.6.4. Special Populations: Are Proxy-Reports Ever Appropriate?

There are numerous situations in which patients are not physically or cognitively able to provide direct assessment of their experience. Obvious examples include infants and small children, individuals with significant cognitive impairment (congenital or acquired), and those at end-of-life. In such settings, proxy-reports of QoL are often collected,[20] though the literature suggests that proxy-reports demonstrate moderate agreement, at best, with patient-reports.[84-86] Nevertheless, proxy-reports are viewed as valuable in many of these settings because caregiver or family perception is also an important consideration. The FDA strongly discourages proxy-reports in product-labeling claims.[10] Unfortunately, such an extreme stance leaves these vulnerable populations marginalized. By not considering proxy-reports, symptom-based research and other lines of inquiry in these populations face considerable obstacles with a potential end-result that drugs or products that could improve symptom burden or QoL never have the opportunity to gain FDA approval for such indications. The FDA's position on proxy-reports is emphasized because of the rigorous standard the FDA guidance document establishes, but that position should not devalue the

potential role for proxy-reports. Ideally, the extent of agreement between patient- and proxy-reports can be established in advance of use of proxy reports. The PROMIS Initiative is investigating application of existing methods for PROs to proxy-reports to improve performance.[87,88]

4.7. Implementation Issues

Upon successful navigation of the challenging process of selecting PRO instruments and the mode of administration comes the daunting task of implementing the selected instruments. Below is a practical framework for successful implementation, centered on achieving data quality and consistency.

Just as with mode of administration, implementing PRO data collection is best achieved if consistency is a central tenet, especially if the registry study is multicenter. In this setting, consistency refers to processes. Standard operating procedures should be established for each site of data collection that delineate, to the extent possible, how patients, researchers, and clinicians interact with the collection system (paper or electronic). As part of standard operating procedures, specific training should be provided, with accessible and easy-to-use manuals available (preferably in both text and video format). Every aspect of the process that can be standardized should be standardized, including the dataset itself. That is, the datasets should include metadata that describe key components important for subsequent analyses and end-users, including who completed the instrument (patient or proxy), where it was completed (e.g., outpatient clinic, home, inpatient ward), which version was administered, and a flag for irregularities identified as part of internal quality control.

Ideally, for multisite studies, these standard operating procedures are the same at each site, with another set of standard operating procedures for the central repository (or coordinating) site that delineates how often data from cooperating sites should be transmitted, how it should be compiled and stored, how often it should undergo quality assessment, and how it should be accessed and distributed for analysis. Within multisite registries, and even within some single site registries, it may be necessary to select an instrument that has been translated into and validated in other languages besides English. It is not adequate to simply translate an instrument into another language, as the psychometric properties obtained within an American population of patients with disease X are unlikely to be reproduced in a population of Japanese patients with the same disease. Thus, formal assessment of the psychometric properties of the instrument is necessary when translating to another language.

Another aspect of consistency in this setting reflects administering the same instrument over the lifespan of the registry. The strength of this recommendation depends partly upon the purpose of the registry; for registries comparing effectiveness, this consistency is essential, while for a registry focused on quality and embedded within an EHR, this recommendation is less stringent. Nevertheless, if the data are collected prospectively, the strong preference is for consistency in PRO instrument administered. Regardless of purpose, collected data should include metadata labels.

Further, involving the entire healthcare team (physicians, mid-level providers, nurses, administrators, and other support staff) in the development process is essential, especially with respect to integrating the PRO instruments into the clinical workflow and providing clinician feedback. As part of this integration, clinical triggers should be established (and standardized) that explicitly force acknowledgement of a patient report by a provider (e.g., a pain score of 8 out of 10) or initiate some standardized intervention (e.g., a patient reporting a high distress level might be automatically contacted by a psychosocial care support team).[87] Such standardized triggers will only be embraced if there is inclusion of the healthcare

team in the implementation process. This inclusive implementation process will also help shape the perception of the PRO data, in that buy-in from the healthcare team will make the PRO collection process a necessary and desired component of care, rather than simply an extra task to complete.[87]

Finally, explicitly including the patient voice in the form of PROs has been shown to improve patient well-being and enhance patient-provider communication.[35] Building on this premise, inclusion of PROs in observational studies may improve patient engagement, recruitment, and retention, though there are no data directly supporting this. The experience of the Duke Cancer Care Research Program with ePRO collection as part of routine cancer care has shown remarkable response and participation rates, with rates of missing data, even for sensitive questions such as level of sexual enjoyment, routinely less than 5% (manuscript in preparation). Certainly, more rigorous documentation of improved long-term patient participation with inclusion of PROs is needed before more ardent assertions can be made.

4.8. Summary Regarding Selecting PRO Instruments

Selecting PRO instruments for inclusion in registry studies is not a one-size-fits-all process. The Center for Medical Technology Policy prepared a guidance document for inclusion of PROs in adult oncology trials[39] and these recommendations are included as an example (Table 8). Clear and careful definition of the target population, concept to be measured, and purpose of the registry is an important first step. For a given population or context, even in a registry, it is important to have some *a priori* hypotheses and justification for outcomes being measured, or the study risks becoming a prospective fishing expedition. As such, there needs to be a systematic approach to selecting salient outcomes (to the extent possible in a registry, which admittedly is sometimes exploratory by nature). In CER, the process of identifying meaningful outcomes requires upfront patient input. But regardless of how the outcomes are selected, there must be a systematic approach to determining whether an outcome is best reported by a patient (i.e., if information about a particular symptom or overall health state or satisfaction is sought, it is best reported from the patient/surrogate perspective, thus a PRO instrument is appropriate). Far too frequently, the tail wags the dog in registry studies; that is, PRO instruments are selected first, prior to identifying outcomes of interest. Thus, the rational identification of outcomes of interest early in the process of registry development is important. Such an approach will quickly identify if PROs are appropriate and will produce a sound base for evaluating PRO instruments and administration methods. If this process is navigated effectively, the stage will be set for successful incorporation of PROs into the registry.

After the arduous process of clearly defining the population and outcomes of interest, search for existing PRO instruments that will assess the outcomes of interest. (See Case Examples 7, 8, 9, and 10.) If a suitable measure is not identified, options include modifying an existing measure or developing a new measure. (See Case Example 7.) In general, development of new PRO instruments is resource intense, so it is preferable to use an existing measure whenever possible. After identifying (or developing) a measure, administration mode should be selected. Electronic administration is preferred, but not all instruments have been evaluated using electronic administration, though this can be accomplished. Important to the scientific basis of the registry are the psychometric properties of the instrument. While the FDA highly values content validity, it is possible to effectively use an instrument with modest content validity, depending on the purpose of the registry, highlighting the importance of understanding and defining the purpose of the registry.

In most registry studies, the purposes of the study and outcomes of interest will necessitate inclusion of PRO data. Careful planning is essential, in identifying appropriate PRO instruments for inclusion, selecting modes of instrument administration, and implementing the PRO collection system, and when done effectively, this generally produces more complete datasets that truly include the voices of all stakeholders in the healthcare system and are meaningful to all stakeholders.

5. Example of PRO Use in a Registry

Consider the division of pulmonary medicine at an academic university. Within the division is a growing multidisciplinary cystic fibrosis (CF) program with a large catchment area and approximately 250 patients ranging in age from 21-65 years, though most patients are younger than age 35. As the program develops, the team plans to implement a series of initiatives targeting not only improved survival, but also improved functioning for patients with CF. Proposed interventions include routine endocrinology consultations for all CF-related diabetes mellitus, improved psychological services, and standardized exercise regimens during hospitalizations. The outcomes of interest for these interventions are equally broad ranging, but include traditional measures such as pulmonary function (as measured by pulmonary function tests), end-organ damage (diabetes, chronic kidney disease), resistant organism colonization rates, hospitalization utilization, symptom burden (including breathlessness, weight change, worry, and fatigue) and quality of life (QoL). The team plans to use a registry for this because they do not feel that they can reasonably test the effectiveness of these interventions through parallel or sequential randomized, controlled trials, but do wish to systematically capture outcomes of interest in a longitudinal manner as the interventions are introduced.

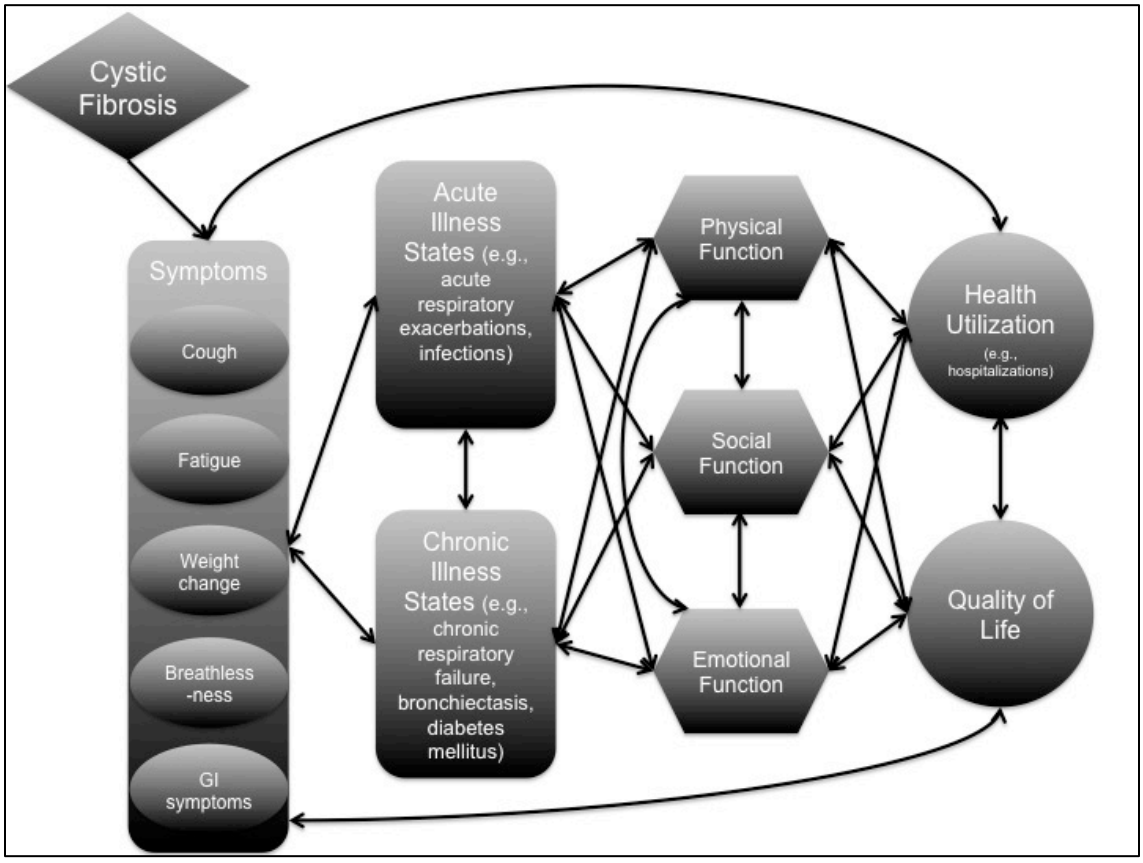
In considering the outcomes of interest, symptom burden, and health-related QoL merit closer inspection for inclusion of PROs. Certainly, patients are better positioned to report breathlessness, worry, fatigue, and QoL. In fact, most argue that patients are the only valid source of information on these issues, thus inclusion of PROs in this registry is appropriate.

In considering which instruments to use, it is important for the team to consider the relationships between the symptoms under consideration and QoL. Figure 3 illustrates some of the relationships that exist around health-related quality of life in cystic fibrosis. Specifically, the influence of symptom burden on QoL must be weighed carefully, to help determine if a series of single-item instruments is most appropriate or if a multi-item, disease-specific instrument (of which there are several in CF) or another approach is most appropriate. As the team plans to use this registry in a longitudinal fashion for numerous planned interventions and because they want to understand how specific interventions impact certain domains impacted by CF, they select an established, multi-item, multi-domain, CF-specific measure that incorporates an aggregate assessment of QoL, as well as several component domains of well-being.

Since the planned settings of intervention include both inpatient and outpatient settings and because of travel issues related to the catchment area, the team also plans to capture reports between visits, such that no more than two months elapse between PRO data collection. For this reason, the team prefers to use electronic methods, but the instrument they selected has only been psychometrically assessed via paper-based methods. They collaborate with the institutional expert on PROs to document paper-electronic equivalence, and to perform usability and feasibility testing for web-based administration. This pilot study demonstrates that it is reasonable to use a web-based approach for PRO assessments.

From a health-care team standpoint, implementation goes smoothly, since the entire CF team was involved in developing the registry and PRO system. Missing data are minimal for inpatient and clinic appointment collection, as the team heavily advertised the PRO collection system to the patients prior to implementation, provided in-clinic teaching, and used reports during the clinical visits; the instrument quickly becomes viewed as a necessary component to the healthcare encounter. However, as data accumulates, the team identifies patterns in missing data for between-visit administrations. They identify that at-home internet access remains a problem for a small but significant portion of their patients. They receive a grant from the local CF foundation to support internet access for vulnerable patients, with subsequent reduction in missing data.

Figure 3. Simplified Concept Map



This example highlights several key points: 1) the importance of understanding the target population; 2) the need to identify outcomes of interest prior to selecting PRO instruments as the outcomes of interest should dictate the instrument, not vice versa; 3) the benefit of incorporating PRO instruments into longitudinal, routine care.

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Case Examples for Chapter 5

Case Example 7. Developing and Validating a Patient-Administered Questionnaire

Description	The Benign Prostatic Hypertrophy (BPH) Registry & Patient Survey was a multicenter, prospective, observational registry examining the patient management practices of primary care providers and urologists, and assessing patient outcomes, including symptom amelioration and disease progress. The registry collected patient-reported and clinician-reported data at multiple clinical visits.
Sponsor	sanofi-aventis
Year Started	2004
Year Ended	2007
No. of Sites	403
No. of Patients	6,928

Challenge

Lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) have a strong relationship to sexual dysfunction in aging males. Sexual dysfunction includes both erectile dysfunction (ED) and ejaculatory dysfunction (EjD), and health care providers treating patients with symptoms of BPH should evaluate men for both types of dysfunction. Providers can use the Male Sexual Health Questionnaire (MSHQ), a validated, self-administered, sexual function scale, to assess dysfunction, but the 25-item scale can be perceived as too long. To assess EjD more efficiently, it was necessary to develop a brief, patient-administered, validated questionnaire.

Proposed Solution

The team used representative, population-based samples to develop a short-form scale for assessing EjD. The team administered the 25-item MSHQ to three populations: a sample of men from the Men's Sexual Health Population Survey, a subsample of men from the Urban Men's Health Study, and a sample of men enrolled in the observational registry.

Using the data from the sample populations, the team conducted a series of analyses to develop the scale. The team used factor analysis to help select the items from the scale that had the highest correlations with the principal factors. Using conventional validation, the team examined reliability (both internal consistency and test-retest repeatability). To assess validity, tests of repeatability and discriminant/convergent validity were used to determine that the short form successfully discriminated between men with no to mild LUTS/BPH and those with moderate to severe LUTS/BPH. Lastly, the team examined the correlation between the 7-item ejaculation domain of the 25-item MSHQ and the new short-form scale using data from the observational registry.

Results

Based on the results of these analyses, the team selected three ejaculatory function items and one ejaculation bother item for inclusion in the new MSHQ-EjD Short Form. The new scale demonstrates a high degree of internal consistency and reliability, and it provides information to identify men with no to mild LUTS/BPH and those with moderate to severe LUTS/BPH.

Key Point

Developing new instruments for collecting patient-reported outcomes requires careful testing of the new tool in representative populations to ensure validity and reliability. Registries can provide a large sample population for validating new instruments.

For More Information

Rosen RC, Catania JA, Althof SE. et al. Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. Urology. 2007;69(5):805–9.

Rosen R, Altwein J, Boyle P. et al. Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male. Eur Urol. 2003;44:637–49.

Case Example 8. Using Validated Measures to Collect Patient-Reported Outcomes

Description	The Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD) is a household panel registry designed to assess the prevalence and incidence of diabetes mellitus and cardiovascular disease; disease burden and progression; risk predictors; and knowledge, attitudes, and behaviors regarding health in the U.S. population. The study involves three distinct phases: an initial screening survey, a baseline survey, and yearly followup surveys for 5 years.
Sponsor	AstraZeneca Pharmaceuticals LP
Year Started	2004
Year Ended	2009
No. of Sites	Not applicable
No. of Patients	More than 211,000 individuals were included in the screening survey; approximately 15,000 individuals were followed for 5 years.

Challenge

The SHIELD registry used survey methodologies to collect health information from a large sample of adults. The goal of the study was to capture participants' perspectives and views on diabetes and cardiovascular disease, risk factors for the diseases, and burden of the diseases. The study investigators, noting that treatment for diabetes and cardiovascular disease relies heavily on patient self-management, felt that it was particularly important to gather information on activities, weight control, health attitudes, quality of life, and other topics directly from the participant, without a physician as an intermediary. The investigators also wanted to follow participants over time to better understand disease progression and changes in health behaviors or activities.

To achieve the study goals, the registry needed to collect health-related data directly from participants in such a way that the data would be reliable, valid, and comparable across participant groups and over time.

Proposed Solution

The investigators decided to use validated, patient-reported outcomes measures (PROs) to collect information on health status and behaviors. The PROs allowed the data from the registry to be compared with data collected in other registries to assess the generalizability of data on the study population. In addition, the PROs already took into account issues such as recall bias and interpretability of the questions, and self-administered instruments eliminated the possibility of introducing interviewer bias.

The registry included seven PROs: (1) the 12-item Short Form Health Survey (SF-12) and European Quality of Life (EuroQoL) EQ-5D instrument, to assess health-related quality of life; (2) the Sheehan Disability Scale, to assess the level of disruption in work, social life, and family/home life; (3) the 9-item Patient Health Questionnaire, to assess depression; (4) the Work Productivity and Activity Impairment Questionnaire: General Health, to assess work productivity and absenteeism; (5) the Diet and Health Knowledge Survey; (6) the Press-Ganey Satisfaction questionnaire; and (7) the International Physical Activity Questionnaire, to assess health-related physical activity and sedentary behaviors.

The investigators considered many factors, such as length, ease of use, format, and scoring system, when selecting the PROs to include in the survey. For example, a major reason for selecting the SF-12 rather than the SF-36 as a measure of quality of life was the length of the forms (12 vs. 36 items). The survey is entirely paper based, with participants mailing back completed forms. The validated scoring algorithms are used to account for missing or illegible values on the completed forms. All participants must be able to read and write in English.

Results

The registry had a generally high response rate for the surveys. The response rates were 63.7 percent for the screening survey, 71.8 percent for the baseline survey, and between 71 and 75 percent for the annual surveys. In terms of missing data, participants who return the survey forms tended to complete all of the questions in the appropriate manner. However, the registry is missing longitudinal data from some participants. For example, a participant may have returned the completed form in 2005, failed to return the form in 2006, and returned the form again in 2007. The investigators must account for the missing 2006 values when conducting longitudinal analyses. The data from the survey have been sufficient to support comparisons over time and across participant groups, leading to several publications.

Key Point

Utilization of standardized, validated instruments in a registry can offer many benefits, including enhanced scientific rigor, the ability to compare patient views over time, and the ability to compare registry data with data from other sources to assess the representativeness of the registry population. It should be noted that significant initial planning is necessary to identify appropriate PROs, obtain the

necessary permissions, and include them in a registry. Issues with missing data must be considered in the planning phases for a registry. This registry considered missing data within returned survey questionnaires. In addition, an acceptable followup rate should be stated a priori so that response rates can be better interpreted with respect to their potential for introducing bias.

For More Information

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Grandy S, Chapman RH, Fox KM, et al. Quality of life and depression of people living with type 2 diabetes mellitus and those at low and high risk for type 2 diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). Int J Clin Pract 2008;62:562–8.

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Case Example 9. Challenges in the Collection of PROs in a Longitudinal Registry

Description	A longitudinal registry of men with metastatic castrate-resistant prostate cancer is being conducted among men receiving outpatient care at the Memorial Sloan-Kettering Cancer Center, Oregon Health and Science University, and John Hopkins School of Medicine.
Sponsor	U.S. Department of Defense
Year Started	2012
Year Ended	Ongoing
No. of Sites	3
No. of Patients	Planned enrollment is 400 men with castrate-resistant prostate cancer

Challenge

Regulatory and government agencies and cancer organizations, including the U.S. Food and Drug Administration (FDA), National Cancer Institute, and the American Cancer Society, recommend collecting patient-reported outcomes (PRO) data to capture cancer patients' perspectives on and experiences of their symptoms, disease status and functioning, and health-related quality of life. Collecting PRO data is important for diseases such as cancer, to fully evaluate the benefit and risk profile of potentially toxic oncology treatments. To this end, industry sponsors and the FDA wish to include symptom endpoints in clinical trials but currently lack sufficient information about optimal methods to design robust endpoints. Many challenges to designing PRO endpoints exist, such as identifying appropriate and validated instruments, ensuring interpretability of the data's clinical significance, and having information on the variability of symptoms in order to accurately determine necessary sample sizes. The collection of PRO data presents additional challenges, including identifying the optimal mode(s) of administration, minimizing patient burden, and minimizing incomplete or missing PRO questionnaires.

Proposed Solution

Investigators are using a registry to evaluate longitudinal PRO data among men with metastatic castrate-resistant prostate cancer (mCRPC). mCRPC is characterized by disease progression (continued elevated prostate-specific antigen [PSA] or radiographic progression) regardless of first-line androgen depletion therapy. Many patients with bone metatases experience debilitative symptoms, such as bone pain, in addition to treatment toxicities. The purpose of the registry is to collect PRO and clinical data to inform the development of pain endpoints for future oncology clinical trials that conform to regulatory standards of the FDA and the European Medicines Agency. The registry does not seek to develop a new PRO, but instead to advance methods for administering and interpreting PRO results, as well as to validate a PRO measure of analgesic medication use. Specifically, the goals of the registry are to identify (1) the clinical significance of pain score changes, (2) the average time to pain progression, (3) the proportion of men with pain starting new lines of treatment, (4) appropriate recall periods for pain assessment, and (5) the comparison of methods for quantifying analgesic use.

Results

Registry participants will include 400 patients with metastatic castrate-resistant prostate cancer who are receiving outpatient care between 2012 and 2014 at one of the three institutions. Clinical data, including diagnosis, treatment, and resource utilization, will be abstracted from medical records every three months. Patient-reported data, including pain, analgesic use, and other symptoms, will be collected every six weeks by an automated telephone survey. A key feature of this registry is the use of a single centralized survey platform that includes a phone survey completed by patients and a Web interface through which study staff at participating sites can enter patient medical record data on a quarterly basis. The integrated system of data collection is intended to reduce the burden of data management. The registry is designed in a way which addresses the challenges of collecting longitudinal PRO data, including (1) the importance of electronic PRO assessment and choosing the best mode (e.g., phone, Web-based) of assessment, (2) choosing the optimal frequency and length of each assessment, and (3)

using automated reminders, clear instruction sheets, and survey questions relevant to patients to ensure high survey completion rates.

Key Point

To ensure appropriate clinical interpretation and quality of PRO data, registries can be used to evaluate PRO instrument characteristics and collect data necessary to develop PRO endpoints for use in clinical trials. Addressing operational barriers such as mode of administration, instrument length and frequency, and missing PRO data will improve patient-reported data for use in endpoint development, clinical trials, treatment decision-making, and routine patient care.

For More Information

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Case Example 10. Collecting PRO Data in a Sensitive Patient Population

Description	The Cedars-Sinai Psychiatric Treatment Outcome Registry (CS-PTR) is a single-site patient registry that tracks the outcomes of psychiatric interventions in a naturalistic clinical setting using measurement-based care and patient-reported outcomes.
Sponsor	Cedars Sinai Medical Center
Year Started	2005
Year Ended	2012
No. of Sites	1
No. of Patients	2,600

Challenge

Psychiatric disorders are strongly associated with grave impairments in functioning and quality of life (QOL), but most previous research has focused on symptom improvement and has not specifically investigated the extent to which treatment can improve functioning and QOL outcomes.

The Department of Psychiatry and Behavioral Neurosciences at Cedars Sinai Medical Center enrolled consecutive patients presenting for psychiatric evaluation in a patient registry. Demographic information, DSM-IV diagnosis, and current psychiatric comorbidities were obtained by the provider using structure interviewing (the Mini International Neuropsychiatric Interview). Patients completed "self-assessment questionnaires" during their baseline visit and during quarterly follow-up visits. Validated patient-reported outcome (PRO) tools included questionnaires that collected information on

depressive symptom severity (Quick Inventory of Depressive Symptomatology), functioning (Work and Social Adjustment Scale), and QOL (Quality of Life Enjoyment and Satisfaction Questionnaire).

The registry often encountered significant barriers to obtaining self-reported data from psychiatric patients. For example, the baseline and follow-up questionnaires took approximately 20-30 minutes for patients to complete, and many patients were resistant to spending that amount of time completing the questionnaires, as they did not see the value in completing them.

Proposed Solution

Staff at the clinic educated the patients about the value of the self-assessment questionnaires. They explained to patients that the results of the questionnaires would be used to inform their providers' decisions about diagnoses, appropriate treatment, and treatment progress. The staff implemented an appointment scheduling system that built in a 30-minute block of time before patients were seen by a provider, to allow time for them to complete the self-assessment questionnaires. For patients who had trouble completing the written questionnaire independently, clinicians worked with the patients to complete the questionnaire verbally and recorded the answers themselves. During quarterly follow-up visits, clinicians were expected to review the answers and PRO scores with patients, including any trends in symptom severity, functioning, or QOL changes following treatment initiation.

Results

A total of 2,600 patients were enrolled in the registry over the course of seven years. At baseline, patients reported a wide range of symptom severity, which is expected given the nature of consecutive enrollment of patients in the registry with no exclusion criteria. Psychiatric patients tended to report severely low QOL levels especially if they were older, of Hispanic ethnicity, or if they are diagnosed with mood disorders. Baseline analysis also showed that although symptom severity and functional impairments are significantly correlated with lower reported levels of QOL, they only explained a moderate amount of the variance in QOL. The findings point to the critical need to go beyond symptom severity monitoring and include functioning and QOL measures during the course of assessment, treatment, and research of psychiatric disorders. Analysis of follow-up data is ongoing.

Key Point

PROs are important tools for informing treatment decisions. In patient populations where it is particularly difficult to obtain PRO data, operational steps, such as discussing the benefits of PRO, changing appointment time frames, and offering support in completing PRO tools from clinicians or other trained professionals, can be taken to minimize the burden on patients. Regularly reviewing PRO data with patients and informing patients of the value of PRO data to their treatment may increase patients' participation.

For More Information

IsHak WW, Balayan K, Bresee C, et al. A descriptive analysis of quality of life using patient-reported measures in major depressive disorder in a naturalistic outpatient setting. Qual Life Res. 2012 Apr 29. [Epub ahead of print]

Chapter 6. Data Sources for Registries

1. Introduction

Identification and evaluation of suitable data sources should be completed within the context of the registry purpose and availability of the data of interest. A single registry may have multiple purposes and integrate data from various sources. While some data in a registry are collected directly for registry purposes (primary data collection), important information also can be transferred into the registry from existing databases. Examples include demographic information from a hospital admission, discharge, and transfer system; medication use from a pharmacy database; and disease and treatment information, such as details of the coronary anatomy and percutaneous coronary intervention from a catheterization laboratory information system, electronic medical record, or medical claims databases. In addition, observational studies can generate as many hypotheses as they test, and secondary sources of data can be merged with the primary data collection to allow for analyses of questions that were unanticipated when the registry was conceived.

This chapter will review the various sources of both primary and secondary data, comment on their strengths and weaknesses, and provide some examples of how data collected from different sources can be integrated to help answer important questions.

2. Types of Data

The types of data to be collected are guided by the registry design and data collection methods. The form, organization, and timing of required data are important components in determining appropriate data sources. Data elements can be grouped into categories identifying the specific variable or construct they are intended to describe. One framework for grouping data elements into categories follows:

- *Patient identifiers*: Some registries may use patient identifiers to link data. In these registries, data elements are linked to the specific patient through a unique patient identifier or registry identification number. The use of patient identifiers may not be possible in all registries due to privacy regulations. (See Chapter 7.)
- *Patient selection criteria*: The eligibility criteria in a registry protocol or study plan determine the group that will be included in the registry. These criteria may be very broad or restrictive, depending on the purpose. Criteria often include demographics (e.g., target age group), a disease diagnosis, a treatment, or diagnostic procedures and laboratory tests. Health care provider, health care facility or system, and insurance criteria may also be included in certain types of registries (e.g., following care patterns of specific conditions at large medical centers compared with small private clinics).
- *Treatments and tests*: Treatments and tests are necessary to describe the natural history of patients. Treatments can include pharmaceutical, biotechnology, or device therapies, or procedures such as surgery or radiation. Evaluation of the treatment itself is often a primary focus of registries (e.g., treatment safety and effectiveness over 5 years). Results of laboratory testing or diagnostic procedures may be included as registry outcomes and may also be used in defining a diagnosis or condition of interest.
- *Confounders*: Confounders are elements or factors that have an independent association with the outcomes of interest. These are particularly important because patients are typically not randomized to therapies in registries. Confounders such as comorbidities (disease diagnoses and conditions) can confuse analysis results and interpretation of causality. Information on the health

care provider, treatment facility, concomitant therapies, or insurance may also be considered. Unknown confounders, or those not recorded in the registry, pose particular challenges for the analysis of patient outcomes. If external, or linked, data sources may provide values for these confounder variables otherwise not in the registry, they may ultimately help reduce bias in the analysis and interpretation of patient outcomes.

- *Outcomes*: The focus of this document is on patient outcomes. Outcomes are end results and are defined for each condition. Outcomes may include patient-reported outcomes (PROs). In some registries, surrogate markers, such as biomarkers or other interim outcomes (e.g., hemoglobin A1c levels in diabetes) that are highly reflective of the longer term end results are used.

Before considering the potential sources for registry data, it is important to understand the types of data that may be collected in a registry. Several types of data that may be gathered from other sources in some registries are described below.

Cost/resource utilization—Cost and/or resource utilization data may be necessary to examine the cost-effectiveness of a treatment. Resource utilization data reflect the resources consumed (both services and products), while cost data reflect a monetary value assigned to those resources. Examples include the actual cost of the treatment (e.g., medication, screening, procedure) and the associated costs of the intervention (e.g., treatment of side effects, expenses incurred traveling to and from clinicians' appointments). Costs that are avoided due to the treatment (e.g., the cost to treat the avoided disease) and costs related to lost workdays may also be important to collect, depending on the objectives of the study. Registries that collect cost data over long periods of time (i.e., many years) may need to adjust costs for inflation during the analysis phase of the study. The types of data elements included in this framework are further described in Chapter 4 and below with respect to their source or the utility of the data for linking to other sources. Many of these may be available through data sources outside of the registry system.

Patient identifiers—Depending on the data sources required, some registries may utilize certain personal identifiers for patients in order to locate them in other databases and link the data. For example, Social Security Numbers (SSNs) in combination with other personal identifiers can be utilized to identify individuals in the National Death Index (NDI). Patient contact information, such as address and phone numbers, may be collected to support tracking of participants over time. Information for additional contacts (e.g., family members) may be collected to support followup in cases where the patient cannot be reached. In many cases, patient informed consent and appropriate privacy authorizations are required to utilize personal identifiers for registry purposes, and the use of personal identifiers may not be possible in some registries; Chapter 7 discusses the legal requirements for including patient identifiers. Systems and processes must be in place to manage security and confidentiality of these data. Confidentiality can be enhanced by assigning a registry-specific identifier via a crosswalk algorithm, as discussed below. Demographics, such as date of birth (to calculate age at any time point), gender, and ethnicity, are typically collected and may be used to stratify the registry population.

Disease/condition—Disease or condition data include those related to the disease or condition of focus for the registry and may incorporate comorbidities. Elements of interest related to the confirmation of a diagnosis or condition could be date of diagnosis and the specific diagnostic results that were used to make the diagnosis, depending on the purpose of the registry. Disease or condition is often a primary eligibility or outcome variable in registries, whether the intent is to answer specified treatment questions (e.g., measure effectiveness or safety) or to describe the natural history. This information may also be

collected in constructing a medical history for a patient. In addition to "yes" or "no" to indicate presence or absence of the diagnosis, it may be important to capture responses such as "missing" or "unknown."

Treatment/therapy—Treatment or therapy data include specific identifying information for the primary treatment (e.g., drug name or code, biologic, device product or component parts, or surgical intervention, such as organ transplant or coronary artery bypass graft) and may include information on concomitant treatments. Dosage (or parameters for devices), route of administration, and prescribed exposure time, such as daily or three times weekly for four weeks, should be collected. Pharmacy data may include dispensing information, such as the primary date of dispensation and subsequent refill dates. Data in device registries can include the initial date of dispensation or implantation and subsequent dates and specifics of required evaluations or modifications. Compliance data may also be collected if pharmacy representatives or clinic personnel are engaged to conduct and report pill counts or volume measurements on refill visits or return visits for device evaluations and modifications.

Laboratory/procedures—Laboratory data include a broad range of testing, such as blood, tissue, catheterization, and radiology. Specific test results, units of measure, and laboratory reference ranges or parameters are typically collected. Laboratory databases are becoming increasingly accessible for electronic transfer of data, whether through a system-wide institutional database or a private laboratory database. Diagnostic testing or evaluation may include procedures such as psychological or behavioral assessments. Results of these procedures and clinician exam procedures may be difficult to obtain through data sources other than the patient medical record.

Biosamples—The increased collection, testing, and storage of biological specimens as part of a registry (or independently as a potential secondary data source such as those described further below) provides another source of information that includes both information from genetic testing (such as genetic markers) and actual specimens.

Health care provider characteristics—Information on the health care provider (e.g., physician, nurse, or pharmacist) may be collected, depending on the purpose of the registry. Training, education, or specialization may account for differences in care patterns. Geographic location has also been used as an indicator of differences in care or medical practice.

Hospital/clinic/health plan—System interactions include office visits, outpatient clinic visits, emergency room visits, inpatient hospitalizations, procedures, and pharmacy visits, as well as associated dates. Data on all procedures as defined by the registry protocol or plan (e.g., physical exam, psychological evaluation, chest x-ray, CAT scan), including measurements, results, and units of measure where applicable, should be collected. Cost accounting data may also be available to match these interactions and procedures. Descriptive information related to the points of care may be useful in capturing differences in care patterns and can also be used to track patterns of referral of care (e.g., outpatient clinic, inpatient hospital, academic center, emergency room, pharmacy).

Insurance—The insurance system or payer claims data can provide useful information on interactions with the health care systems, including visits, procedures, inpatient stays, and costs associated with these events. When using these data, it is important to understand what services were covered under the various insurance plans at the time the data were collected, as this may affect utilization patterns.

3. Data Sources

Data sources are classified as primary or secondary based on the relationship of the data to the registry purpose. Primary data sources incorporate data collected for direct purposes of the registry (i.e., primarily for the registry). Primary data sources are typically used when the data of interest are not available elsewhere or, if available, are unlikely to be of sufficient accuracy and reliability for the planned analyses and uses. Primary data collection increases the probability of completeness, validity, and reliability because the registry drives the methods of measurement and data collection. (See Chapter 4.) These data are prospectively planned and collected under the direction of a protocol or study plan, using common procedures and the same format across all registry sites and patients. The data are readily integrated for tracking and analyses. Since the data entered can be traced to the individual who collected them, primary data sources are more readily reviewed through automated checks or followup queries from a data manager than is possible with many secondary data sources.

Secondary data sources are comprised of data originally collected for purposes other than the registry under consideration (e.g., standard medical care, insurance claims processing). Data that are collected as primary data for one registry would be considered secondary data from the perspective of a second registry if linking were done. These data are often stored in electronic format and may be available for use with appropriate permissions. Data from secondary sources may be used in two ways: (1) the data may be transferred and imported into the registry, becoming part of the registry database, or (2) the secondary data and the registry data may be linked to create a new, larger dataset for analysis. This chapter primarily focuses on the first use for secondary data, while Chapters 16, 17, and 18 discuss the complexities of linking registries with other databases.

When considering secondary data sources, it is important to note that health professionals are accustomed to entering the data for defined purposes, and additional training and support for data collection are not required. Often, these data are not constrained by a data collection protocol and they represent the diversity observed in real-world practice. However, there may be increased probability of errors and underreporting because of inconsistencies in measurement, reporting, and collection. Staff changes can further complicate data collection and may affect data quality. There may also be increased costs for linking the data from the secondary source to the primary source and dealing with any potential duplicate or unmatched patients.

Sufficient identifiers are also necessary to accurately match data between the secondary sources and registry patients. The potential for mismatch errors and duplications must be managed. (See Case Example 37.) The complexity and obligations inherent in the collection and handling of personal identifiers have previously been mentioned (e.g., obligations for informed consent, appropriate data privacy, and confidentiality procedures).

Some of the secondary data sources do not collect information at a specific patient level but are anonymous and intended to reflect group or population estimates. For example, census tract or ZIP-Code-level data are available from the Census Bureau and can be merged with registry data. These data can be used as "ecological variables" to support analyses of income or education when such socioeconomic data are missing from registry primary data collection. The intended use of the data elements will determine whether patient-level information is required.

The potential for data completeness, variation, and specificity must be evaluated in the context of the registry and intended use of the data. It is advisable to have a solid understanding of the original purpose of the secondary data collection, including processes for collection and submission, and verification and validation practices. Questions to ask include: Is data collection passive or active? Are standard definitions or codes used in reporting data? Are standard measurement criteria or instruments utilized (e.g., diagnoses, symptoms, quality of life)? The existence and completeness of claims data, for example, will depend on insurance company coverage policies. One company may cover many preventive services, whereas another may have more restricted coverage. One company may cover a treatment without restriction, while another may require prior authorization by the physician or require that the patient must have first failed on a previous, less expensive treatment. Also, coverage policies can change over time. These variations must be known and carefully documented to prevent misinterpretation of use rates. Additionally, secondary data may not all be collected in the format (e.g., units of measure) required for registry purposes and may require transformation for integration and analyses.

An overview of some secondary data sources that may be used for registries is given below. Table 9 identifies some key strengths and limitations of the identified data sources.

Table 9. Key Data Sources – Strengths and Limitations

Data Source	Strengths and Uses	Limitations
Patient-reported data	• Patient and/or caregiver outcomes. • Unique perspective. • Obtaining information on treatments not necessarily prescribed by clinicians (e.g., over-the-counter drugs, herbal medications). • Obtaining intended compliance information. • Useful when timing of followup may not be concordant with timing of clinical encounter.	• Literacy, language, or other barriers that may lead to underenrollment of some subgroups • Validated data collection instruments may need to be developed. • Loss to followup or refusal to continue participation. • Limited confidence in reporting clinical information and utilization information.
Clinician-reported data	• More specific information than available from coded data or medical record	• Clinicians are highly sensitive to burden. • Consistency in capture of patient signs, symptoms, use of nonprescribed therapy varies.

Data Source	Strengths and Uses	Limitations
Medical Chart abstraction	• Information on routine medical care, with more clinical context than coded claims. • Potential for comprehensive view of patient medical and clinical history. • Use of abstraction and strict coding standards (including handling missing data) increases the quality and interpretation of data abstracted.	• The underlying information is not collected in a systematic way. For example, a diagnosis of bacterial pneumonia by one physician may be based on a physical exam and patient report of symptoms, while another physician may record the diagnosis only in the presence of a confirmed laboratory test. • It is difficult to interpret missing data. For example, does absence of a specific symptom in the visit record indicate that the symptom was not present or that the physician did not actively inquire about this specific symptom or set of symptoms? • Data abstraction is resource intensive. • Complete medical and clinical history may not be available (e.g., new patient to clinic).
Electronic health records (EHRs)	• Information on routine medical care and practice, with more clinical context than coded claims. • Potential for comprehensive view of patient medical and clinical history. • Efficient access to medical and clinical data. • Use of data transfer and coding standards (including handling of missing data) will increase the quality of data abstracted.	• Underlying information from clinicians is not collected using uniform decision rules. (See example under “Medical chart abstraction.”) • Consistency of data quality and breadth of data collected varies across sites. • Difficult to handle information uploaded as text files into the EHRs (e.g., scanned clinician reports) vs. direct entry into data fields. • Historical data capture may require manual chart abstraction prior to implementation date of medical records system. • Complete medical and clinical history may not be available (e.g., new patient to clinic). • EHR systems vary widely. If data come from multiple systems, the registry should plan to work with each system individually to understand the requirements of the transfer.

Data Source	Strengths and Uses	Limitations
Institutional or organizational databases	• Diagnostic and treatment information (e.g., pharmacy, laboratory, blood bank, radiology). • Resource utilization (e.g., days in hospital). • May incorporate cost data (e.g., billed and/or paid amounts from insurance claims submissions).	• Important to be knowledgeable about coding systems used in entering data into the original systems. • Institutional or organizational databases vary widely. The registry should plan to work with each system individually to understand the requirements of the transfer.
Administrative Databases	• Useful for tracking health care resource utilization and cost-related information. • Range of data includes anything that is reimbursed by health insurance, generally including visits to physicians and allied health providers, most prescription drugs, many devices, hospitalization(s), if a lab test was performed, and in some cases, actual lab test results for selected tests (e.g., blood test results for cholesterol, diabetes). • In some cases, demographic information (e.g., gender, date of birth from billing files) can be uploaded. • Potential for efficient capture of large populations.	• Represents clinical cost drivers vs. complete clinical diagnostic and treatment information. • Important to be knowledgeable about the process and standards used in claims submission. For example, only primary diagnosis may be coded and secondary diagnoses not captured. In other situations, value-laden claims may not be used (e.g., an event may be coded as a “nonspecific gynecologic infection” rather than a “sexually transmitted disease”). • Important to be knowledgeable about data handling and coding systems used when incorporating the claims data into the administrative systems. • Can be difficult to gain the cooperation of partner groups, particularly in regard to receiving the submissions in a timely manner.

Data Source	Strengths and Uses	Limitations
Death Indexes	• Completeness—death reporting is mandated by law in the United States. • Strong backup source for mortality tracking (e.g., patient lost to followup). • National Death Index (NDI)—centralized database of death records from State vital statistics offices; database updated annually. • NDI causes of death relatively reliable (93–96 percent) compared with State death certificates. • Social Security Administration's (SSA) Death Master File—database of deaths reported to SSA; database updated weekly.	• Time delay—indexes depend on information from other data sources (e.g., State vital statistics offices), with delays of 12 to 18 months or longer (NDI). It is important to understand the frequency of updates of specific indexes that may be utilized. • Absence of information in death indexes does not necessarily indicate "alive" status at a given point in time. • Most data sources are country specific and thus do not include deaths that occurred outside of the country. • Death Master File no longer includes protected state records as of November 2011.
U.S. Census bureau databases	• Population data. • Core census survey conducted every decade. • Wide range in specificity of information from U.S. population down to neighborhood and household level. • Useful in determining population estimates (e.g., numbers, age, family size, education, employment status).	• Targets participants via survey sampling methodology and estimates. • Does not provide subject-level data.
Existing registries	• Can be merged with another data source to answer additional questions not considered in the original registry protocol or plan. • May include specific data not generally collected in routine medical practice. • Can provide historical comparison data. • Reduces data collection burden for sites, thereby encouraging participation.	• Important to understand the existing registry protocol or plan to evaluate data collected for element definitions, timing, and format, as it may not be possible to merge data unless many of these aspects are similar. • Creates a reliance on the other registry. • Other registry may end. • Other registry may change data elements (which highlights the need for regular communication). • Some sites may not participate in both. • Must rely on the data quality of the other registry.

Medical chart abstraction—Medical charts primarily contain information collected as a part of routine medical care. These data reflect the practice of medicine or health care in general and at a specific level (e.g., geographical, by specialty care provider). Charts also reflect uncontrolled patient behavior (e.g., noncompliance). Collection of standard medical practice data is useful in looking at treatments and outcomes in the real world, including all of the confounders that affect the measurement of effectiveness (as distinguished from efficacy) and safety outside of the controlled conditions of a clinical trial. Chart documentation is often much poorer than one might expect, and there may be more than one patient-specific medical record (e.g., hospital and clinical records). A pilot collection is recommended for this labor-intensive method of data collection to explore the availability and reproducibility of the data of interest. It is important to recognize that physicians and other clinicians do not generally use standardized data definitions in entering information into medical charts, meaning that one clinician's documented diagnosis of "chronic sinusitis" or "osteoarthritis" or description of "pedal edema" may differ from that of another clinician.

Electronic health records—The use of electronic health records (EHRs), sometimes called electronic medical records (EMRs), is increasing. EHRs have an advantage over paper medical records because the data in some EHRs can be readily searched and integrated with other information (e.g., laboratory data). The ease with which this is accomplished depends on whether the information is in a relational database or exists as scanned documents. An additional challenge relates to terminology and relationships. For example, including the term "fit" in a search for patients with epilepsy can yield a record for someone who was noted as "fit," meaning "healthy." Relationships can also be difficult to identify through searches (e.g., "Patient had breast cancer" vs. "Patient's mother had breast cancer"). The quality of the information has the same limitations as described in the paragraph above. Both the availability and standardization of EHR data have grown significantly in recent years, and this trend is expected to continue. As of 2009, some data suppliers cited individual datasets exceeding 10 million lives.[1] More recently, data suppliers are reporting 20 million[2] to 35 million[3] patients in their datasets. Further, it is anticipated that more significant standardization of EHR data will result from the "EHR certification" requirements being developed in phases under the American Recovery and Reinvestment Act of 2009 (ARRA). Such standardization should increase not only the availability and utility of EHR records, but also the ability to aggregate them into larger data sources.

Institutional or organizational databases—Institutional or organizational databases may be evaluated as potential sources of a wide variety of data. System-wide institutional or hospital databases are central data repositories, or data warehouses, that are highly variable from institution to institution. They may include a portion of everything from admission, discharge, and transfer information to data reflecting diagnoses and treatment, pharmacy prescriptions, and specific laboratory tests. Laboratory test data might be chemistry or histology laboratory data, including patient identifiers with associated dates of specimen collection and measurement, results, and standard "normal" or reference ranges. Catheterization laboratory data for cardiac registries may be accessible and may include details on the coronary anatomy and percutaneous coronary intervention. Other organizational examples are computerized order entry systems, pharmacies, blood banks, and radiology departments.

Administrative databases—Private and public medical insurers collect a wealth of information in the process of tracking health care, evaluating coverage, and managing billing and payment. Information in the databases includes patient-specific information (e.g., insurance coverage and copays; identifiers such as name, demographics, SSN or plan number, and date of birth) and health care provider descriptive data (e.g., identifiers, specialty characteristics, locations). Typically, private insurance companies organize health care data by physician care (e.g., physician office visits) and hospital care (e.g., emergency room visits, hospital stays). Data include procedures and associated dates, as well as costs charged by the provider and paid by the insurers. Amounts paid by insurers are often considered proprietary and unavailable. Standard coding conventions are utilized in the reporting of diagnoses, procedures, and other information. Coding conventions include the Current Procedure Terminology (CPT) for physician services and International Classification of Diseases (ICD) for diagnoses and hospital inpatient procedures. The databases serve the primary function of managing and implementing insurance coverage, processing, and payment. (See Case Example 11.)

Medicare and Medicaid claims files are two examples of commonly used administrative databases. The Medicare program covers over 43 million people in the United States, including almost everyone over the age of 65, people under the age of 65 who qualify for Social Security Disability, and people with end-stage renal disease.[4] The Medicaid program covers low-income children and their mothers; pregnant women; and blind, aged, or disabled people. As of 2007, approximately 40 million people were covered by Medicaid.[5] Medicare and Medicaid claims files, maintained by the Centers for Medicare & Medicaid Services (CMS), can be obtained for inpatient, outpatient, physician, skilled nursing facility, durable medical equipment, and hospital services. As of 2006, Medicare claim files for prescription drugs can also be obtained. The claims files generally contain person-specific data on providers, beneficiaries, and recipients, including individual identifiers that would permit the identity of a beneficiary or physician to be deduced. Data with personal identifiers are clearly subject to privacy rules and regulations. As such, the information is confidential and to be used only for reasons compatible with the purpose(s) for which the data are collected. The Research Data Assistance Center (ResDAC), a CMS contractor at the University of Minnesota, provides assistance to academic, government, and nonprofit researchers interested in using Medicare and/or Medicaid data for their research.[6]

Death and birth records—Death indexes are national databases tracking population death data (e.g., the NDI[7] and the Death Master File [DMF] of the Social Security Administration [SSA][8]). Data include patient identifiers, date of death, and attributed causes of death. These indexes are populated through a variety of sources. For example, the DMF includes death information on individuals who had an SSN and whose death was reported to the SSA. Reports may come in to the SSA by different paths, including from survivors or family members requesting benefits or from funeral homes. Because of the importance of tracking Social Security benefits, all States, nursing homes, and mortuaries are required to report all deaths to the SSA. Prior to 2011, the DMF contained virtually 100-percent complete mortality ascertainment for those eligible for SSA benefits. As of November 2011, however, the DMF no longer includes protected state death records. In practical terms, this means that approximately 4.2 million records were removed from the historical public DMF (which contained 89 million records), and some 1 million fewer records will be added to the DMF each year.[9] The NDI can be used to provide both fact of death and cause of death, as recorded on the death certificate. Cause-of-death data in the NDI are relatively reliable (93–96 percent) compared with death certificates.[10 11] Time delays in death reporting should be considered when using these sources, and vital status should not be assumed to be alive by the

absence of information at a recent point in time. These indexes are a valuable source of data for death tracking. Of course, mortality data can be accessed directly through queries of State vital statistics offices and health departments when targeting information on a specific patient or within a State. Likewise, birth certificates are available through State departments and may be useful in registries of children or births.

Area-level databases—Two sources of area-level data are the U.S. Census and the Area Resource File (ARF). The U.S. Census Bureau databases[12] provide population-level data utilizing survey sampling methodology. The Census Bureau conducts many different surveys, the main one being the population census. The primary use of the data is to determine the number of seats assigned to each State in the House of Representatives, although the data are used for many other purposes. These surveys calculate estimates through statistical processing of the sampled data. Estimates can be provided with a broad range of granularity, from population numbers for large regions (e.g., specific States), to ZIP Codes, all the way down to a household level (e.g., neighborhoods identified by street addresses). Information collected includes demographic, gender, age, education, economic, housing, and work data. The data are not collected at an individual level but may serve other registry purposes, such as understanding population numbers in a specific region or by specific demographics. The ARF is maintained by the Health Resources and Services Administration, which is part of the Department of Health and Human Services. The ARF includes county-level data on health facilities, health professions, measures of resource scarcity, health status, economic activity, health training programs, and socioeconomic and environmental characteristics.[13]

Provider-level databases—Data on medical facilities and physicians may be important for categorizing registry data or conducting subanalyses. Two sources of such data are the American Hospital Association's Annual Survey Data and the American Medical Association's Physician Masterfile Data Collection. The Annual Survey Data is a longitudinal database that collects 700 data elements, covering organizational structure, personnel, hospital facilities and services, and financial performance, from more than 6,000 hospitals in the United States.[14] Each hospital in the database has a unique ID, allowing the data to be linked to other sources; however, there is a data lag of about 2 years, and the data may not provide enough nuanced detail to support some analyses of cost or quality of care. The Physician Masterfile Data Collection contains current and historic data on nearly one million physicians and residents in the United States. Data on physician professional medical activities, hospital and group affiliations, and practice specialties are collected each year.

Encounter-level databases—Databases of individual patient encounters (e.g., physician office visits, emergency department visits, hospital inpatient stays), generally do not contain individual patient identifiers and thus may not be linkable to patient registries, but nevertheless provide valuable insight into the makeup of the registry's target population. This is particularly true for data from nationally representative surveys, such as AHRQ's Health Care Utilization Project (H-CUP) Nationwide Inpatient Sample (NIS) and the suite of surveys by the Centers for Disease Control (CDC) and National Center for Health Statistics (NCHS), including the National Ambulatory Medical Care Survey (NAMCS), the National Hospital Ambulatory Medicare Care Survey (NHAMCS), and the National Hospital Discharge Survey (NHDS).

Existing registry and other databases—There are numerous national and regional registries and other databases that may be leveraged for incorporation into other registries (e.g., disease-specific registries

managed by nonprofit organizations, professional societies, or other entities). An example is the National Marrow Donor Program (NMDP),[15] a global database of cord blood units and volunteers who have consented to donate marrow and blood cells. Databases maintained by the NMDP include identifiers and locators in addition to information on the transplants, such as samples from the donor and recipient, histocompatibility, and outcomes. NMDP actively encourages research and utilization of registry data through a data application process and submission of research proposals. The Registry of Patient Registries (RoPR) may be a useful resource for finding existing registries (www.patient-registries.com).

In accessing data from one registry for the purposes of another, it is important to recognize that data may have changed during the course of the source registry, and this may or may not have been well documented by the providers of the data. For example, in the United States Renal Data System (USRDS),[16] a vital part of personal identification is CMS 2728, an enrollment form that identifies the incident data for each patient as well as other pertinent information, such as the cause of renal failure, initial therapy, and comorbid conditions. Originally created in 1973, this form is in its third version, having been revised in 1995 and again in 2005. Consequently, there are data elements that exist in some versions and not others. In addition, the coding for some variables has changed over time. For example, race has been redefined to correspond with Office of Management and Budget directives and Census Bureau categories. Furthermore, form CMS 2728 was optional in the early years of the registry, so until 1983 it was filled out for only about one-half of the subjects. Since 1995, it has been mandatory for all persons with end-stage renal disease. These changes in form content, data coding, and completeness would not be evident to most researchers trying to access the data.

4. Other Considerations for Secondary Data Sources

The discussion below focuses on logistical and data issues to consider when incorporating data from other sources. Chapter 11 fully explores data collection, management, and quality assurance for registries.

Before incorporating a secondary data source into a registry, it is critical to consider the potential impact of the data quality of the secondary data source on the overall data quality of the registry. The potential impact of quality issues in the secondary data sources depends on how the data are used in the primary registry. For example, quality would be significant for secondary data that are intended to be populated throughout the registry (i.e., used to populate specific data elements in the entire registry over time), particularly if these populated data elements are critical to determining a primary outcome. Quality of the secondary data would have less effect on overall registry quality if the secondary data are to be linked to registry data only for a specific analytic study (see Chapter 18). For more information on data quality, see Chapter 11.

The importance of patient identifiers for linking to secondary data sources cannot be overstated. Multiple patient identifiers should be used, and primary data for these identifiers should not be entered into the registry unless the identifying information is complete and clear. While an SSN is very useful, high-quality probabilistic linkages can be made to secondary data sources using various combinations of such information as name (last, middle initial, and first), date of birth, and gender. For example, the NDI will make possible matches when at least one of seven matching conditions is met (e.g., one matching condition is "exact month and day of birth, first name, and last name"). However, the degree of success in such probabilistic and deterministic matching generally is enhanced by having many identifiers to facilitate matching. As noted earlier, the various types of data (e.g., personal history, adverse events,

hospitalization, and drug use) have to be linked through a common identifier. A discussion of both statistical and privacy issues in linkage is provided in Chapter 16, and a discussion of managing patient identity across systems is provided in Chapter 17.

The best identifier is one that is not only unique but has no embedded personal identification, unless that information is scrambled and the key for unscrambling it is stored remotely and securely. The group operating the registry should have a process by which each new entry to the registry is assigned a unique code and there is a crosswalk file to enable the system to append this identifier to all new data as they are accrued. The crosswalk file should not be accessible by persons or entities outside the management group.

In addition, consideration should be given to the fact that a registry may need to accept and link datasets from more than one outside organization. Each institution contributing data to the registry will have unique requirements for patient data, access, privacy, and duration of use. While having identical agreements with all institutions would be ideal, this may not always be possible from a practical perspective. Yet all registries have resource constraints, and decisions about including certain institutions have to be determined based on the resources available in order to negotiate specialized agreements or to maintain specialized requirements. Agreements should be coordinated as much as possible so that the function of the registry is not greatly impaired by variability among agreements. All organizations participating in the registry should have a common understanding of the rules regarding access to the data. Although exceptions can be made, it should be agreed that access to data will be based on independent assessment of research protocols and that participating organizations will not have individual veto power over access.

When data from secondary sources are utilized, agreements should specify ownership of the source data and clearly permit data use by the recipient registry. The agreements should also specify the roles of each institution, its legal responsibilities, and any oversight issues. It is critical that these issues and agreements be put in place before data are transferred so that there are no ambiguities or unforeseen restrictions on the recipient registry later on.

Some registries may wish to incorporate data from more than one country. In these cases, it is important to ensure that the data are being collected in the same manner in each country or to plan for any necessary conversion. For example, height and weight data collected from sites in Europe will likely be in different units than height and weight data collected from sites in the United States. Laboratory test results may also be reported in different units, and there may be variations in the types of pharmaceutical products and medical devices that are approved for use in the participating countries. Understanding these issues prior to incorporating secondary data sources from other countries is extremely important to maintain the integrity and usefulness of the registry database.

When incorporating other data sources, consideration should also be given to the registry update schedule. A mature registry will usually have a mix of data update schedules. The registry may receive an annual update of large amounts of data, or there could be monthly, weekly, or even daily transfers of data. Regardless of the schedule of data transfer, routine data checks should be in place to ensure proper transfer of data. These should include simple counts of records as well as predefined distributions of key variables. Conference calls or even routine meetings to go over recent transfers will help avoid mistakes that might not otherwise be picked up until much later. An example of the need for regular communication is a situation that arose with the United States Renal Data System a few years ago. The

United Network for Organ Sharing (UNOS) changed the coding for donor type in their transplant records. This resulted in an apparent 100-percent loss of living donors in a calendar year. The change was not conveyed to USRDS and was not detected by USRDS staff. After USRDS learned about the change, standard analysis files that had been sent to researchers with the errors had to be replaced.

Distributed data networks are another model for sharing data. In a distributed data network, data sharing may be limited to the results of analyses or aggregated data only. There is much interest in the potential of distributed data networks, particularly for safety monitoring or public health surveillance (see Chapter 15.11). However, the complexities of data sharing within a distributed data network are still being addressed, and it is premature to discuss good practice for this area.

5. Summary

In summary, a registry is not a static enterprise. The management of registry data sources requires attention to detail, constant feedback to all participants, and a willingness to make adjustments to the operation as dictated by changing times and needs.

References for Chapter 6

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Case Examples for Chapter 6

Case Example 11. Using Claims Data along with Patient-Reported Data to Identify Patients

Description	The National Amyotrophic Lateral Sclerosis (ALS) Registry is a rare disease registry created by the Agency for Toxic Substances and Disease Registry (ATSDR) within the U.S. Department of Health and Human Services (HHS). The purpose of the registry is to quantify the incidence and prevalence of ALS in the U.S., describe the demographics of persons with ALS, and examine potential risk factors for the disease.
Sponsor	U.S. Department of Health and Human Services and Agency for Toxic Substances and Disease Registry, through funding from the "ALS Registry Act" (U.S. Congress Public Law 110-373).
Year Started	2010
Year Ended	Ongoing
No. of Sites	All 50 states, including U.S. territories; data from national administrative databases are combined with patient self-enrollment data.
No. of Patients	The first year of complete registry data (calendar year 2011) is anticipated for release in winter 2013 and will consist of a de-identified, non-duplicate dataset.

Challenge

Amyotrophic Lateral Sclerosis (ALS) is a progressive, fatal neurodegenerative disorder of both the upper and lower motor neurons. Many knowledge gaps exist in the understanding of ALS, including uncertainty about the disease incidence and prevalence, misdiagnosis of ALS in patients with other motor neuron disorders, and the role of environmental exposures in the etiology of ALS. Because ALS is a non-reportable disease in the U.S. (except for the state of Massachusetts), previous attempts to estimate ALS incidence and prevalence using non-specific mortality data have faced many challenges and at best overestimated disease frequency. Identifying patients through site recruitment for research purposes poses additional challenges, as access to patient medical records can be limited, costly, and time-consuming to obtain. Patient recruitment issues are compounded by the complexities of this rare disease, in which the average timeframe from diagnosis to death is 2-5 years. U.S. governmental agencies acknowledged that a national, structured data collection program for ALS was greatly needed and alternate data sources and recruitment strategies would need to be identified.

Proposed Solution

In 2008, President Bush signed the ALS Registry Act into law, allowing ATSDR to create the National ALS Registry. The registry is the only Congressionally-mandated population-based ALS registry in the United States. As a first step in developing the registry, a workshop of international experts in neurological and autoimmune conditions was convened to discuss approaches to creating a national database. Based on feedback from these experts, the registry uses a two-pronged approach to identify all U.S. cases of ALS. The first approach utilizes national administrative databases, including Medicare, Medicaid, Veterans Health Administration, and Veterans Benefit Administration, to identify prevalent cases based on an algorithm developed through pilot projects. These administrative databases cover approximately 90

million Americans, and the algorithm identifies 80-85% of all true ALS cases when applied to these databases. The second approach uses a secure web-portal to allow patients to self-enroll voluntarily. Data from the two approaches are combined into the registry database, and duplicate patients are identified and removed so that each person with ALS is only counted once in the registry.

Results

The registry data will support several research projects. The web-portal for self-enrolled participants contains brief surveys that collect information on potential risk factors, such as socio-demographic characteristics, occupational history, military history, cigarette, smoking, alcohol consumption, physical activity, family history of neurodegenerative diseases, and disease progression. ATSDR is also currently implementing active surveillance projects that will allow population-based case estimates of ALS in certain smaller geographic areas (i.e., at the state and metropolitan levels) to help ATSDR evaluate the completeness of the registry. In addition, ATSDR has developed a system to inform persons with ALS about new research (e.g., clinical trials, epidemiologic studies) for which they may be eligible. Lastly, ATSDR is funding a feasibility study for the creation of a national biospecimen repository that would be open to all U.S. residents with ALS enrolled in the registry. This proposed biorepository will help researchers to better understand the disease because it will pair biospecimans (e.g., blood, brain tissue) with existing risk factor data from patients.

Key Point

Combining multiple data sources, such as administrative databases and patient-reported information, is a novel approach and can be an effective means to successfully identify patients with a rare disease and to better understand the prevalence, incidence, and etiology of the disease. However, using alternative approaches requires a strong understanding of the nuances of the individual data sources; pilot testing is also helpful to identify potential issues with data sources prior to registry launch.

For More Information

http://www.cdc.gov/als/

Section II. Legal and Ethical Considerations for Registries

Chapter 7. Principles of Registry Ethics, Data Ownership, and Privacy

This chapter discusses the ethical and legal considerations that should guide the development and use of patient registries. The chapter reviews the Common Rule, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and other relevant U.S. laws and regulations.

Currently, this chapter is being updated to address the omnibus final rule implementing many changes to HIPAA, which is scheduled for release in the summer of 2012. The revised chapter will be posted for public comment separately in the fall of 2012.

Chapter 8. Informed Consent for Registries

1. Introduction

This chapter identifies the best practices for obtaining informed consent for registry participation. It builds on some of the general ethical and legal principles discussed in the "Principles of Registry Ethics, Data Ownership, and Privacy" chapter, specifically the application of the regulations governing human subjects research and the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.

The purpose of this chapter is to provide an ethical framework for obtaining informed consent for registry participation and to distinguish registries from clinical research protocols. It is not designed to provide specific legal guidance, nor can it substitute for Institutional Review Board (IRB) review. Moreover, where law is discussed it is limited to U.S. statutes and, more specifically, to Federal as opposed to state regulations. Some states have guidelines governing the conduct of research involving human subjects or statutes addressing privacy, and an exploration of either area is beyond the scope of this chapter. Likewise, analysis of the relevant international standards and laws is left to others. Case Examples 12 and 13 provide descriptions of practical issues that registries have encountered in this area.

2. Registries, Research, and Other Activities

The purpose of this volume is to provide guidance for *registries used to evaluate patient outcomes,* such as efforts to describe the natural history of disease, determine clinical and/or cost effectiveness, assess safety or harm, and measure or improve quality of care. As a result, the focus of this chapter is on informed consent issues that arise in registries used for research. Some registries used for research may have been developed initially for clinical purposes (e.g., a name/contact information registry of patients using a particular treatment to facilitate notifications or recalls). Increasingly, however, registries are being used for research purposes even when initially developed for clinical purposes, and thus it is suggested that in all cases, consideration should be given to the informed consent issues, as well as HIPAA privacy requirements, discussed in this chapter. The HIPAA Privacy Rule governs the use and disclosure of most individually identifiable health information (called protected health information or "PHI") held by covered entities (health plans, health care clearinghouses, and most health care providers).

The Federal research regulations promulgated by the U.S. Department of Health and Human Services (HHS), as well as those developed by U.S. Food and Drug Administration (FDA), focus on clinical research involving human subjects. The FDA regulations apply to "all clinical investigations" regulated by the FDA—defined as "any experiment that involves a test article and one or more human subjects".[1] The HHS regulations apply only to "human subjects research," where "research" is defined as a "systematic investigation" and "human subject" as a living person about whom the investigator obtains either data through intervention or interaction, or identifiable private information.[2] Thus, investigations that involve non-living individuals, or that do not collect data through intervention/interaction and do not collect identifiable information are not governed by the HHS regulations. Despite the apparent limitations of the regulatory language, institutions may choose to apply the frameworks more broadly (sometimes under an "assurance," i.e., an agreement with HHS that the institution will apply the regulations to all research at the institution regardless of funding source). Even when the activity in question meets the HHS definition of research subject to regulation, a series of exemptions may apply.[3]

2.1. Registry Research vs. Clinical Research

It is worth noting some of the significant differences between registry research and clinical research. In particular, the use of a control group in a registry setting is often substantively different from the concept of a control group in a clinical research setting. Registry controls may be pulled from a general population—in some cases a population that may not have interacted with health professionals or a health institution. Unlike clinical controls, who may be exposed to placebos (and thus need to consent) or exposed to a standard treatment (and thus will already be involved in the treatment system), registry controls may be identified from an unaffected population. This raises ethical questions about the initial contact with an individual who may have no link to the registry topic area and who may view the contact as an unwelcome intrusion or perhaps even an incorrect indication of problematic health status.[4] Furthermore, since a clinical research trial may involve double-blind procedures, "controls" may agree to participate because of the potential for direct therapeutic benefits or even the indirect therapeutic benefits that come from better attendant care. In other situations, controls may participate because they hope to help others suffering from their ailments (altruistic reasoning) or perhaps because they seek monetary compensation. In contrast, controls in a registry trial have no similar potential therapeutic (direct or indirect) or monetary benefits. While altruism may play a role in this context, its effects may be less than ideal. There is a great concern about the potential for selection bias in the creation of a control group for registry trials (there is also significant concern about the effect of bias in clinical trials). Those who may agree to participate in a registry may be qualitatively different from those who do not agree, which can threaten the external validity of research findings. Concerns about selection bias will be heightened for diseases with a low prevalence in the general population since there will be a greater possibility that the bias will affect the data. Developing consent requirements in such a way as to avoid selection bias will be extremely important in this setting.

Questions about adapting the regulatory requirements to research that does not fit the typical clinical model are not unusual. There are two other areas that have raised questions about the how the Federal regulations apply and that are particularly relevant to registry evaluations: public health activities and quality improvement/assurance (QI/QA).

2.2. Public Health Activities

The HIPAA Privacy Rule expressly permits the disclosure of Protected Health Information (PHI) to a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, including for activities related to disease, injury, or vital event reporting. Thus, a covered entity may disclose PHI, without individual authorization, for a registry maintained by a public health authority (or by an entity acting under a grant of authority from or contract with such public agency) for authorized public health purposes, such as, for example, immunization registries, state cancer registries, birth and death registries, and general disease reporting (although the latter is often anonymous). The HIPAA Privacy Rule also allows the disclosure of PHI to a person subject to the jurisdiction of FDA for FDA regulated product reporting.

Public health activities may not be considered "human subjects research" under HHS or FDA regulations. Differentiating between public health practice and public health research activities can be challenging. According to the Belmont Report, on which the Federal research regulations are based, if any aspect of an activity constitutes "research" then the entire activity should undergo regulatory review. The Office for Human Research Protections (OHRP) interpretation of the HHS regulations implies that if any part of the

activity falls under the regulations the entire activity is covered.[5] By contrast, the Centers for Disease Control and Prevention (CDC) only consider an activity research if the primary intent is to contribute to or generate generalizable knowledge.[6] The CDC, however, does not provide official interpretations of HHS regulations, as this is the role of OHRP. Local IRB policies in this area vary; some focus on whether the primary intent of an activity is to gain generalizable knowledge, and others categorically exclude normal public health department activities.

To address confusion regarding what is considered a public health activity versus a research activity, the Council of State and Territorial Epidemiologists (CSTE) issued a report clarifying that public health practice activities are those for which: there is a specific or general legal authorization to conduct (e.g., state statutory cancer registries, or reports of newborn hearing screening to the state health department); the specific intent of the authority conducting the activity is to promote the health of, or prevent harm to, the individuals or communities involved (as opposed to research where the intent is to gather generalizable knowledge); and there are, in fact, health benefits to the individuals involved or to the target community.[7] Moreover, public health activities, unlike research, are not likely to involve experimental procedures or to have one (or more) individuals responsible for the development and conduct of the activity such as a primary investigator (PI), or entail individual randomization for access to interventions.

Alternatively, a public health activity may fit the definition of research, but fall into one of the various exemptions to covered research. For example, there are exemptions for research involving surveys, interviews, or observations of public behavior, provided certain requirements are met.[8] There is also an exemption for the collection or examination of existing data, if publicly available and information is recorded "in such a manner that subjects cannot be identified, directly or through identifiers."[9]

2.3. Quality Improvement/Quality Assurance Activities

As with certain public health activities, HIPAA provides an explicit exception to the authorization requirements for the use and disclosure of PHI for "health care operations," which are defined as certain activities of a covered entity, including "conducting quality assessment and improvement activities…, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities."[10] Individual authorization for disclosure of PHI in this context is not necessary, but individual consent is permitted if a covered entity chooses to obtain it.

The Federal research regulations do not have an explicit exemption for QI/QA activities. Many of the efforts in this area will: (a) not meet the regulatory definitions of "research," (b) not involve "human subjects," (c) fall under a delineated exemption, or (d) not be supported by HHS, involve an FDA regulated product, or otherwise covered by an assurance of compliance. Some local IRBs appear to consider all QI/QA activities outside the scope of the regulations, as they might public health activities.

The application of the human subjects research regulations does not rest on whether or not a procedure is considered "standard" or part of the "standard of care;" rather, it rests on the purpose of the activity. Intent to publish the results of a QI/QA activity is not determinative of whether the human subjects regulations apply. Registries developed within an institution to implement a practice to improve the quality of patient care or to collect data regarding the implementation of such a practice are not considered "research" under the regulations. Nor are registries designed to collect provider performance data for clinical, practical, or administrative uses. Registries that involve existing data that is not individually identifiable may entail "research," but do not involve "human subjects" as defined by the

HHS regulations; therefore the HHS regulations do not apply. However, a QI/QA project that involves an untested clinical intervention (whether or not part of the standard of care) for purposes of gathering scientific evidence of efficacy (i.e., a systematic investigation designed to contribute to generalizable knowledge) would be governed by the regulations, although a specific exemption may apply (e.g., if it is part of the evaluation of a public benefit program).[11] Even if the regulations apply, waivers or alterations to the consent process may be approved as noted below.

3. Current Challenges for Registries

3.1. Electronic Health Records

The development of large-scale data registries raises a variety of regulatory questions, and this is nowhere more evident than in the discussions about electronic health records (EHRs). These issues are explored in detail in Chapter 15. This chapter focuses only on the relevant consent issues. There are currently few, if any, efforts to obtain individual consent for the creation of an EHR (or, for that matter, the creation of any health record). Yet, these databases have enormous research potential. For example, Kaiser Permanente, a leader in the use of health information technology, created and maintains one of largest private-sector EHR systems, collecting health information from over 8.7 million Kaiser members nationwide. Moreover, there are a number of efforts to develop (sometimes via state legislation) multi-payer claims registries to support comparative effectiveness research (CER). Various steps have been discussed to ensure the privacy and confidentiality of the individual health information gathered into these registries (e.g., the use of coded identifiers). Application of traditional consent models for the secondary use of these databanks for research may prove inefficient and may result in selection bias, impacting the usefulness of downstream analyses.

As the development of EHRs, claims registries, health information exchanges, and linkages between innumerable health databases moves forward, keeping records private becomes more difficult to manage. Personal health information may be accessed and shared in ways patients never imagined, often for the purpose of secondary analysis and often without patient consent. Although studies consistently indicate that Americans are generally supportive of EHRs and even secondary uses of the data, they want to be informed about how and to what extent their information will be shared and disclosed to others.[12,13,14,15]

Despite apparent public unease with a system of open access to EHRs, the Institute of Medicine (IOM) in 2009 released a statement that informed consent for research using EHRs should not be required, with the justification that obtaining permission from patients is too burdensome for researchers and should be eliminated entirely.[16] This generated widespread concern that the IOM's proposal would undermine the trust that forms the basis of the patient-physician relationship and also more broadly increased concerns about patients' privacy and confidentiality protections. Given the strong arguments on both sides, establishing consensus on the topic has been slow.

In an effort to resolve the debate, additional work in this area should focus on striking the appropriate balance between providing patients with control over information and facilitating necessary research. Commentators have suggested a variety of different approaches, including recognition of public ownership of large electronic databases[17] or the creation of licensed data centers that would control access to information without individual consent.[18] It is not clear from the empirical evidence that patients want full consent protections in this context. One study, for example, found that patients were more likely to be comfortable with the research uses of their EHR information when they were asked about the use by a

specific entity (e.g., universities, hospitals, or disease foundations) rather than when asked in the abstract, and that they fully supported public health uses of their data.[19] Public education about the scope of research uses may alleviate some patient concerns about the use of EHR data without consent.[20] Similarly, addressing underlying fears about unauthorized access to identifiable data or discriminatory uses of the information can also be helpful in increasing support for this type of research. Given the vast potential for using EHRs to conduct large-scale observational studies, development of an alternative to specific individual consent may be useful. On July 26, 2011, HHS and the Office of Science and Technology Policy (OSTP) published an advance notice of proposed rulemaking (ANPRM) entitled, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators."[21] A number of changes have been proposed to enhance protections of research participants, while facilitating valuable research and reducing burden among research investigators. Included in the proposal are suggestions that specifically address EHRs and large-scale electronic databanks.

3.2. Biobanks

The increasing availability of electronic data repositories linked with biological samples (and biobank registries) raises additional concerns. In addition to the Federal regulations described below, there are also guidelines governing the creation of a data repository or biobank (see Chapter 7). In particular, IRBs are charged with reviewing protocols for obtaining, storing and sharing information; verifying informed consent; and protecting privacy and confidentiality.

The Secretary's Advisory Committee on Human Research Protection (SACHRP) advises the Secretary of HHS on issues related to the protection of human subjects. SACHRP developed frequently asked questions (FAQs) to provide a framework for IRBs, institutions, and investigators to consider relating to the collection, use, and storage of biospecimens.[22] One of the FAQs states that generally consent is necessary before moving excess identifiable clinical specimens to a centralized databank. In rare circumstances, an IRB may determine that the conditions for a waiver of consent have been met. Relevant factors to consider include: governance and oversight of bank; protections in place for confidentiality/privacy; policies regarding access to specimens; nature of research for which specimens used; ability to locate/contact subjects; risk of introducing bias into collection; potential anxiety/confusion for subjects; number of subjects; length of time since specimens first collected; and the likelihood subject would object to research use.[22] While these are designed to address the use of clinical specimens, the issues raised are also applicable to the use of clinical data. Similarly, SACHRP suggests that an IRB determine whether a transfer of specimens to a new bank or institution is permissible under the initial consent—a relevant point for information transfers as well. At this point, the SACHRP recommendations have not yet been implemented by the Secretary of HHS.

As with EHRs, there have been a variety of challenges to the use of biobanks for research without specific individual consent. Many long-standing biobanks were established either for non-research purposes (e.g., newborn blood spot banks) or under a general consent allowing the use of leftover tissue in hospitals. While more recent banks and repositories have been set up with a variety of consent protections, it is unclear what to do with existing repositories created without these protections, or how to manage access to archived data within the repositories where initial consent was either silent on the matter or significantly limits future research. At least one author has suggested the creation of a new regulatory oversight framework that would substitute for the necessary individual informed consent for the use of

existing data or tissue samples.[23] Another suggests using broad initial consents to cover a variety of future uses.[24] Litigation in Texas and Minnesota regarding the use of newborn blood spots has highlighted this issue in the national dialogue, and development of additional regulations at the State level is likely. The ANPRM cited above includes among its proposed changes mechanisms to improve informed consent, including consent for the secondary use of pre-existing biospecimens and data.

Key unresolved issues relevant to both biobanks and large information data repositories include: obligations to return individually relevant research results, future unforeseen research uses, the need to recontact participants (some of whom may not wish to be recontacted or who are deceased), the financial burdens of recontacting, the limits on withdrawal of the sample or information, whether the sample/information can be kept indefinitely, whether commercial uses of the bank should be treated differently than non-commercial uses, and the implications of large-scale database research for socially identifiable groups. Moreover, as technology continues to progress, so will the ability to re-identify participants from data deposited into biobanks and large data repositories.

De-identification and aggregate reporting alone does not completely conceal identity.[25,26] For example, there is a considerable push to make de-identified, aggregate-level data from Genome Wide Association Studies (GWAS) publicly available in large repositories so that the data can be combined with other studies for more powerful analysis. However, an individual can be re-identified by assessing the probability that an individual or relative participated in a GWAS through composite statistics across cohorts (such as allele frequency or genotype counts). BioVU, the Vanderbilt DNA Databank, has taken steps to diminish the risk of re-identification. BioVU is linked to a de-identified version of data extracted from an EHR in which all personal identifiers have been removed. Thus, there is no identifiable information attached to the records. The disadvantages or tradeoffs in such design are that it explicitly precludes both re-contact and linking with any information other than that contained within the original EHR. It also prevents the return of individual results—an issue that remains controversial even when the study design allows it.

The informed consent documents initially used for biobanking research either stated explicitly that no results would be returned to participants or remained silent on the issue. More recently, there is general agreement in the scientific community supporting the return of aggregate results to research participants. There is less agreement on return of individual results. Moreover, there is still debate regarding the most ethically appropriate mechanisms for returning results (e.g., when, how, and by whom-- physician or investigator). In 2010 a National Heart, Lung, and Blood Institute (NHLBI) Working Group released revised recommendations providing guidance on many of these issues, but the issue is far from settled.[27]

3.3. Reconsidering the Ethical Framework Governing Research

Perhaps the most challenging part of the shift to large database research and the current regulatory structure is the potential re-framing of the underlying ethical issues. The July 2011 HHS-issued ANPRM states that "[a]lthough the regulations have been amended over the years, they have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimen repositories, and the use of advanced technologies, such as genomics." The current Federal research regulations are based on the Belmont Report, which focused on the traditional clinical research context. The HIPAA Privacy Rule was put in

place more recently to protect the privacy of individually identifiable health information and demonstrates the challenges with balancing individual privacy with the information needs of a comprehensive health system. The future focus on electronic data repositories and the potential for large-scale observational studies to replace some clinical trial data require consideration of whether the approaches used thus far should be adapted.

For example, in discussing the possible use of the FDA's Sentinel System as a pharmacoepidemiological research database, Professor Barbara Evans identified three "novel challenges in applying familiar ethical frameworks."[28] The first is the possibility that with the shorter time period between research results and clinical application, the history categorization of research versus treatment (or even public health practice versus research) may be incorrect. Perhaps IRBs will need to consider both the potential direct medical benefits of an observational study, and potential participant health risks such as negative insurance coverage determinations or changes in physician prescribing patterns. Second, the creation of these massive databanks that span numerous states (and sometimes countries) raises issues about whether the "local context review" that forms the basis for the IRB system continues to be relevant. Although a detailed examination of state regulations is not part of this chapter, it is worth emphasizing the challenges faced by multi-state registries, which may face different requirements for informed consent, different privacy protections, and even different definitions of "human subjects research" from state-to-state. This can add enormous burden to the regulatory oversight system and significant complexity to these endeavors. Finally, this type of research raises questions about the meaning of vulnerability and susceptibility to harm, and who should be identified as a "vulnerable" population in need of additional protections. It may be that the groups traditionally considered vulnerable in the clinical research context are not especially vulnerable in this context. Conversely, there may be groups particularly vulnerable to re-identification, or for whom re-identification poses unique risks of psychosocial or economic harms, but which would not usually be considered vulnerable in clinical research. In fact, the need to understand potential group harms highlights the limitations of the traditional ethical framework that assumes the focus should be on the individual. More work is needed to consider the ethical framework that should guide large-scale observational studies, but such exploration is beyond the scope of this chapter. The challenges raised by these studies have implications for research more generally and may lead to broader regulatory changes such as those proposed in the ANPRM.

4. Regulatory Consent Requirements

While a number of issues remain unanswered in this area, there is some clear guidance for registries that fall under the Federal research regulations. There are two primary sets of Federal regulations governing the conduct of human subjects research. HHS regulates research supported by Federal money or covered under an institutional "assurance of compliance" (see Chapter 7). The FDA regulates research that will be used to support an FDA regulated product. Both sets of regulations largely have the same consent requirements; relevant differences are indicated below. The HIPAA Privacy Rule also contains individual authorization requirements for uses and disclosures of individually identifiable health information for research. Each of these Federal regulatory areas will be discussed in turn.

4.1. HHS and FDA General Consent Requirements

For activities covered by the HHS and FDA research regulations, eight basic elements of information must be provided to research participants:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or whether further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.[29]

In addition, the FDA announced on January 4, 2011 that informed consent forms for applicable clinical trials must include a statement that the trial information will be entered into the National Institutes of Health (NIH) clinical trial registry.[30] Both the HHS and the FDA regulations also require, where appropriate, additional elements of informed consent including:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of research which may related to the subject's willingness to continue participation will be provided to the subject; and
6. The approximate number of subjects involved in the study.[31]

The HHS regulations allow an IRB to approve a waiver or alteration of the consent requirements for minimal risk research where the waiver or alteration will not affect the rights of the subjects, the research cannot be carried out without the waiver, and, when appropriate, subjects will be provided information after participation.[32] The FDA regulations do not allow waivers or alterations under these circumstances, but do allow for waivers in life-threatening situations and allow Presidential waivers for some military

research.[33] Both sets of regulations allow for waiver of consent requirements for research conducted in specific types of emergency situations.[34]

4.2. Documentation and Format of Consent

There are varying requirements for documentation of the consent process. Both FDA and HHS regulations speak to the documentation of informed consent.[35] Unlike treatment consents, research consents are usually written and the consent form functions both as documentation of the consent process, and in some cases as an aspect of the consent itself (since in long form the document contains all of the necessary consent disclosures and participants may be given the form to read as part of the consent process). HHS allows an IRB to waive the written documentation requirement in whole or in part when 1) the only record linking the subject and the research would be the consent document and the principal risk of the study would be potential harm resulting from a breach of confidentiality, or 2) the research involves no more than minimal risk of harm and involves no procedures for which written consent is not normally obtained in a clinical context.[36] In either case, the participant may still be provided a written summary. Waivers may be used to allow oral consent procedures without written documentation. Such an approach is often used in research involving interviews conducted by telephone.

Under certain conditions, an IRB may approve the use of a short form written consent.[37] In these cases, oral presentation of informed consent information is accompanied by a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what has been presented orally. A witness to the oral presentation is required, and the participant (or representative) must be given copies of the short form document and the summary. The participant must sign the short form document and the witness will sign both the short form and the summary.

E-consents may be considered written documentation under either set of regulations and are within the scope of the IRBs' power to authorize as an alternation of written documentation requirements under the HHS regulations. HHS specifically allows electronic signatures on research consent documents, provided they are legally valid in the specific jurisdiction.[38] FDA also has provisions for e-signatures on electronic records, but does not speak directly to e-consent for research participation.[39] While the Federal Electronic Signatures in Global and National Commerce Act (E-SIGN) attempts to provide some uniformity among state laws governing electronic transactions, there remain some variations.[40,41] The primary goals of e-signature laws are authenticating the signature and ensuring privacy and confidentiality of electronic information. Although there have been some suggestions for standardized electronic consent procedures, there is little focused specifically on the research area.[42]

4.3. Informed Consent Form Revisions and Re-consent

Changes to the informed consent document that require re-consent of patients may be necessary if there are changes in the scope of the registry—such as substantive changes to the protocol, addition of procedures not previously addressed in the consent, changes in data sharing or reporting procedures, or if there are identified errors or omissions in the original consent document. As noted below, re-consent may also be necessary if the participants were below the age of consent when initially enrolled but reach the age of majority when the registry is still active (see discussion infra). The decision to change the informed consent form and subsequently re-consent participants needs to be carefully considered due to possible challenges in obtaining the re-consent. For example, participants may be lost to followup because they have moved or died. Challenges may be particularly evident for registries that have been in place for

several years. These difficulties are what prompted the interest in broad general initial consents. In situations where the initial consent does not cover the change, registries may seek IRB waiver of re-consent requirements.

For studies in which re-consent is sought, registry developers should consider the potential effects of selection bias and the implications for external validity. Re-consented participants may be systematically different from non-re-consented participants. For example, participants that are not re-consented may have died or been lost to followup for health related reasons, leaving an overall healthier group of participants. Additionally, even among those who can be contacted, individuals who agree to continue participation may be different from those who refuse to provide consent. As a result, one important requirement for studies that undertake re-consent may be to evaluate characteristics of the original study population as compared to the subset of patients that do re-consent and consider the implications for research outcomes. The evaluation of whether re-consents are more common for particular populations should be done for any analyses that have comparative arms.

Minor changes to a consent document do not necessitate re-consent. Re-consent is necessary, however, where the terms of the study or the background pre-conditions have changed. In some long-term studies, re-informing participants, but not re-consent, may be necessary. Even where re-consent is needed, IRBs may waive requirements. Alternatively, data collection, sharing, and reporting for participants who cannot be re-consented could be maintained in accordance with the terms of the original consent. In those situations in which a re-consent process is implemented, participants should be told the reasons for the re-contact and provided a summary of consent form changes. Additionally, as with the original consent, documentation of the re-consent must be maintained as required by the registry, the IRB, and any relevant regulations.

4.4. Applying the Federal Research Regulations to Registries

Some of the regulatory requirements appear better suited to traditional clinical research trials, rather than registries. For example, of the eight basic elements listed earlier, requirements 4 (alternatives) and 6 (compensation/injury) are crafted to address issues raised in traditional clinical trials, rather than registries. Other elements have aspects that clearly encompass registry research (such as basic elements 1, 2, and 7), but other parts that seem less applicable, since registries will not involve "experimental procedures" that must be identified, entail no physical "discomforts to the subject," and do not pose a risk of (physical) "research-related injury".

Other requirements may pose challenges for registries, such as basic element 8, which requires subjects to be informed about a right to withdraw. While registry participants may refuse to provide additional information about their medical status or care, withdrawing from a registry may undermine the data collection. In situations where the data have been anonymized, withdrawal will likely prove impossible. In many such cases, registry informed consents may contain language notifying subjects that in the event of withdrawal, data that was collected prior to the withdrawal may continue to be used and disclosed according to the consent in order to preserve the scientific integrity of the registry. However, even where data have not been anonymized, some argue that the registry must retain all records to be a valid information tool. The FDA explicitly requires the retention of identifiable data even after a subject withdraws from a study. HHS permits the retention of such data, but also permits the investigator to omit or destroy the data if retention is not required by FDA regulations or study integrity. OHRP suggests that

IRBs provide guidance on documentation of participant withdrawal. Moreover, the OHRP guidance dated September 21, 2010 on this issue clarifies that once a subject withdraws, the investigator must stop interacting with the subject to obtain data, and stop collecting identifiable private information from other sources (unless the subject specifically provides consent to the continued data collection).

4.5. HIPAA

The HIPAA Privacy Rule also may apply to either the use or disclosure of health information into/from a registry, or the use of such information to create a registry, or both. Because the HIPAA Privacy Rule governs the use and disclosure of most individually identifiable health information held by covered entities, the Privacy Rule requirements may apply even if the human subjects research regulations do not. Moreover, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires all qualified entities with which it contracts to provide analyses of drug safety data, regardless of whether they are a HIPAA covered entity, to follow the minimal requirements of the Privacy Rule.[43] Chapter 7 describes the general Privacy Rule framework in this context and the specifics of coverage. The Privacy Rule requires that a covered entity obtain written authorization for the use and disclosure of an individual's PHI for research purposes unless the use or disclosure is permitted by another provision of the Rule (e.g., where a waiver of authorization is applicable). A subject's informed consent to participate in research can be combined with a HIPAA authorization in one document. There are six core elements and three required statements for a HIPAA authorization:

Core Elements

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure
- The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure
- A description of each purpose of the requested use or disclosure
- Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository)
- Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided

Required Statements

- A statement of the individual's right to revoke Authorization in writing, and either: 1) a description of how to do so, and the exceptions to the right to revoke authorization, or 2) reference to the corresponding section of the covered entity's notice of privacy practices.
- Whether treatment, payment, enrollment, or eligibility for benefits can be conditioned on the individual signing the Authorization, including research-related treatment, and consequences of refusing to sign the Authorization, if applicable.

- A statement of the potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.[44]

Authorization is not needed for activities that are "preparatory to research," which may include scanning a patient database to determine feasibility for creating a registry. Before allowing an investigator access to PHI for such purposes, however, the covered entity must obtain from the researcher representations that: 1) the use or disclosure of PHI is sought solely for purposes preparatory to research, 2) no PHI will be removed from the covered entity during the review, and 3) access to the PHI is necessary for the research purposes.[45] These preparatory activities may aid investigators in the identification of potential research participants. Subsequent contact of potential research participants for purposes of obtaining authorization for the use or disclosure of the individual's PHI may be permitted under the Privacy Rule in a variety of ways depending on the relationship between the investigator and the covered entity. An investigator that is a workforce member of the covered entity is permitted to contact potential participants directly or through another person at the covered entity, such as a treating provider, to obtain authorization. Alternatively, a covered entity is permitted to hire a business associate – who may be an investigator – to contact patients to obtain authorization on behalf of the covered entity. Finally, a covered entity is permitted to provide contact information of potential research subjects to an investigator that is not part of the covered entity or a business associate, if the covered entity obtains documentation that an IRB or privacy board has waived the authorization requirement for the disclosure.

Additionally, uses or disclosures of decedents' PHI to a research registry or from a registry for research purposes do not require an authorization (as long as certain representations are provided to the covered entity that is providing the information).[46] Authorizations are also not required for uses or disclosures of de-identified data sets, provided the information has been de-identified in accordance with the Privacy Rule.[47] Nor are authorizations required for uses or disclosures of "limited data sets," as defined by the Rule (so long as a data use agreement is in place with the recipient of the limited data set).[48] See Chapter 7.

In addition, an IRB or privacy board may waive or alter aspects of the HIPAA authorization requirements. Like the requirements for a waiver or alteration under the human subjects research regulations described above, these are limited to situations in which the research could not be practicably carried out both without the waiver or alteration and access to the PHI, and the use or disclosure information involves no more than minimal risk to privacy because there is: (a) an adequate plan to protect the identifiers from improper use or disclosure; (b) an adequate plan to destroy identifiers if possible; and (c) adequate written assurances that the PHI will not be reused or disclosed except as required by law, as needed for research oversight, or for other research in a way permitted by the Privacy Rule.[49]

Finally, if a subject was enrolled in a research protocol prior to the compliance date of the Privacy Rule (for most covered entities, April 14, 2003) and pursuant to a valid informed consent, an authorization may not be required unless after the compliance date another informed consent is sought from the subject.[50] This may be especially relevant to registries that were created prior to the application of the Privacy Rule.

The HIPAA Privacy Rule also speaks to the issue of withdrawal from a registry. The Privacy Rule explicitly gives individuals the right to revoke their authorization for the use and disclosure of protected health information (the revocation must be in writing), except to the extent that a covered entity has

already relied on the authorization. HHS guidance on the application of the Privacy Rule to research makes it clear that a covered entity that has disclosed PHI for research in reliance on an authorization is not required to retrieve information it disclosed prior to receiving the revocation, and may also continue to use and disclose PHI already obtained to the extent necessary to preserve the integrity of the study (e.g., as necessary to account for the subject's withdrawal). As noted above, FDA requires that the data gathered as part of research under their regulatory authority is necessary and must be retained; but even for those registries outside the scope of FDA oversight, HIPAA permits the continued use of data as necessary to protect the integrity of the research.

There is significant focus on coordination and harmonization of the HIPAA authorization requirements and human subjects research informed consent requirements.[51] While a HIPAA authorization may be combined with a research informed consent document (and elements already present in the research consent need not be repeated in the authorization), there are some situations in which an additional separate authorization may be necessary for a separate research activity or future research activity. The HIPAA Privacy Rule allows covered entities to condition the receipt of research-related treatment in a clinical trial on the individual signing an authorization for the use and disclosure of PHI for the trial, and also allows the use of a combined authorization/consent form in this context. However, the Privacy Rule does not currently permit a compound authorization in such circumstances that would also authorize the use or disclose of the individual's PHI for a separate research activity that may not be conditioned on the individual receiving the research-related treatment, such as the use or disclosure of PHI to create or contribute to a separate research database or repository. Thus, a separate authorization would need to be obtained from the individual for the use or disclosure of PHI to the database or repository. Additionally, HHS has determined that HIPAA authorizations must be study-specific for purposes of complying with the Privacy Rule's requirement that an authorization must include a description of each purpose of the requested use or disclosure. Thus, for future uses or disclosures of PHI from a registry maintained by a covered entity, investigators must obtain a new authorization for a specific research purpose, obtain a waiver from the authorization requirements, or otherwise qualify for one of the limited exemptions to the authorization requirement. The latter situation includes those uses or disclosures explicitly permitted by the Privacy Rule (e.g., of de-identified data, of limited data sets with a data use agreement, for public health activities, or for health care operations). HHS published a notice of proposed rulemaking on July 14, 2010, which proposed to both eliminate the prohibition on compound authorizations for conditioned and unconditioned research activities and allow authorizations to encompass certain future research, but these changes have not yet been codified.

4.6. Special Consent Issues: Incapacitated Adults and Children

In addition to the general requirements discussed above, there are also additional requirements for certain specific research populations. HHS has regulations that apply to pregnant women and fetuses, children, and prisoners. FDA has regulations that apply to children (which, for the most part, match the HHS regulations). Both also allow research to be conducted with adults lacking decisional capacity, although consent must be obtained by a "legally authorized representative," who may be a guardian, proxy, or surrogate decision maker (the terms are defined by state law). Likewise, HIPAA also allows for authorizations from "personal representatives" (again, generally defined by state law).

Of particular interest to registries are the research regulations pertaining to children. Unlike research involving adults, research involving children must fit into one of four categories: minimal risk[52], greater

than minimal risk/prospect of direct therapeutic benefit,[53] minor increase over minimal risk/likely to yield generalizable knowledge about subject's disorder or condition,[54] and research not otherwise approvable but authorized by the Secretary of HHS in consultation with an expert panel.[55] Most registry research is likely to fall into the minimal risk category. For these studies, permission must be obtained from at least one parent/guardian and assent obtained from the child, if capable of assenting. Waivers of both permission and assent are possible. Under HHS regulations, a waiver of parental permission is allowed under the same conditions that allow for a waiver of informed consent in adult populations;[56] or when parental permission is not a reasonable requirement to protect the subjects.[57] FDA regulations do not allow for waivers of parental permission. Both HHS and FDA regulations allow a waiver of assent when the research involves an intervention holding the potential for direct therapeutic benefit and is not available except through participation; or when parental permission is waived in accord with section 46.116.[ii,58] Furthermore, when some of all of the children involved are not capable of providing assent, an IRB can determine that assent in not necessary (for the child or children in question, or for all children if appropriate). Both sets of regulations allow an IRB to determine that permission is only required from one parent, even when required from both under 406 or 407, in limited circumstances.[59] Where authorization must be obtained, the HIPAA Privacy Rule requires authorization from only one personal representative of the individual, such as one parent of a minor child, and does not require assent of the child.

OHRP has indicated that when the research in question involves a treatment for which the child would have legal authority to consent, the child's consent may suffice and parental permission may be unnecessary. The HIPAA Privacy Rule also generally provides that when a minor has legal authority to consent to a particular health care service without the involvement of a parent, the minor and not the parent has authority to act as the individual with respect to the PHI pertaining to that health care service. State statutes granting decisionmaking authority to minors vary. Many address issues such as treatment for sexually transmitted infections (STIs), access to contraception, and some even allow consent for mental health or substance abuse treatments. Registries involving these areas may be able to rely on the minor's consent, rather than the parental permission/assent framework. However, more specific legal guidance on the particulars of state statutory interpretation may be warranted in these situations.

Another important consideration is what to do when a minor who is involved in a registry reaches the age of majority. OHRP interprets the continuing consent standard to require that legal consent be sought from the participant upon reaching the age of majority. An authorization under the Privacy Rule, including one signed by a parent as the personal representative of a minor, remains valid until it expires or is revoked, even if such time extends beyond the child's age of majority. If the authorization expires on the date the minor reaches the age of majority, a covered entity would be required to obtain a new authorization signed by the individual in order to further use or disclose PHI covered by the expired authorization. Registries that involve children that will retain identifiable information past the child's age of majority will need to take steps to gain the appropriate consent and, if necessary, authorization for continued use. Less clear is whether investigators should seek a child's assent to continued participation when the initial consent was provided by parents at a time when the child lacked the capacity to play any role in decisionmaking.

[ii] The FDA regulations do not allow waiver of consent by adults, but do allow a waiver of assent requirements if certain requirements are met (and those requirements are the same as the ones that HHS uses for waiving assent—and even waiving consent for adults). 21 CFR 50.55(d).

5. A Proposed Framework for Registry Consents

5.1. Current Practices and Problems

There are three current approaches to consent: opt-in, opt-out, and non-consent. An opt-in approach assumes that an individual will not be part of the registry until they have specifically consented to participation. An opt-out approach assumes that all individuals will be part of a registry, unless there is a specific refusal to participate. Finally, a non-consent model does not seek or require individual consent or refusal, but includes all relevant individuals in a registry. The labeling of the approaches may vary in the literature, but the general concepts remain consistent. Additionally, some registries involve a mix of one or more approaches or a combined consent mechanism, where an opt-in approach is used for one aspect (access to a particular treatment) and non-consent for the other (listing in the treatment registry). This may also be referred to as "conditional access."

5.1.1. Opt-In

An opt-in procedure may involve a consent process similar to that used for clinical research protocols. It may be used separately for a registry, or it may be appended to a consent document used for a particular treatment (for example, individuals who consent to the use of a particular device may also be asked to participate in a registry for that device). While an opt-in approach has the benefit of assuring compliance with the Federal regulations, a number of the regulatory requirements are difficult to apply to registries (as discussed above). This has led many to suggest a modified opt-in approach—using elements of the clinical research framework but adjusting to fit the registry model. But, even with a modified model, there are concerns that the strict informed consent requirements of the clinical research consent will have negative effects on subject selection, resulting in biases that will undermine the validity and thus affect the usefulness of the registry. An analysis of the Canadian Stroke Network estimated that dealing with consent issues cost $500,000 over the first 2-3 years of the registry, and the requirement to obtain written informed consent introduced significant selection biases undermining the usefulness of the registry.[60] Alternative consent approaches may need to be considered for large-scale observational studies.

5.1.2. Opt-Out

An opt-out procedure shifts the presumption from one in which each individual must consent to participate, to one in which each individual must refuse to participate. There is a great deal of discussion about the usefulness of an opt-out model, particularly for registries (e.g., organ donation registries). To be a valid opt-out model, individuals must be fully informed about the existence of the registry and their rights to opt-out of participation. In many cases, the information requirements are the same as the information requirements for an opt-in procedure—the only difference is that instead of explicitly agreeing to participate, the person must take steps explicitly to refuse to participate. While the information requirements may not change, the psychological shift may be significant. If the expectation is that everyone will participate, people may be more inclined to acquiesce. There is evidence in other areas of decisionmaking that setting the default to participation results in greater inclusion than setting the default to non-participation, even when individuals are given an easy way to opt-in or opt-out.[61] While the Federal research regulations appear to assume an opt-in approach, in some circumstances an IRB could approve a modification that allowed a shift to an opt-out. In order for an IRB to approve an opt-out approach for non-exempt, HHS-supported human subjects research, they must document that the waiver of informed consent is appropriate for the research. An opt-out approach may be especially useful for registries. Nonetheless, Privacy Rule requirements will preclude this approach unless the situation fits

within one of the delineated permissible uses without an individual authorization (e.g., with a waiver of authorization for research or for public health activities).

IRBs could consider the opt-out approach for research that meets the four criteria for a waiver or alteration of consent under the HHS guidelines: 1) the research involves no more than minimal risk to participants; 2) the waiver or alteration will not adversely affect the rights and welfare of participants; 3) the research could not practicably be carried out without the waiver or alteration; 4) participants will be provided with additional pertinent information after participation. For example, the Vermont Diabetes Information System (VDIS) is a quality improvement, registry-based decision support and reminder system targeted to primary care physicians and their patients with diabetes. With IRB approval, VDIS incorporated an opt-out consent process.[62] Patients are notified by mail of their eligibility and inclusion in the registry and given a mechanism to opt-out by calling a toll-free number.

5.1.3. Non-Consent

Non-consent is not really a consent mechanism and thus will not be addressed here in detail. Nonetheless, this approach may, and probably should, entail providing participants with information about the registry. The format and process of disclosure may vary. In some cases, general public notifications (perhaps listing on a website, or posting prominently in a place likely to be seen) will be sufficient. In other cases, individual notification may be appropriate. A non-consent approach is used currently for registries that fall outside the Federal research regulations such as state mandated public health reporting or quality improvement activities. One primary methodological advantage of the non-consent approach in no-risk and minimal risk studies is that it can function to reduce concerns about biases introduced by the consent process, such as those that occur when individuals who consent to participate in the registry systematically differ from those who do not or cannot consent. Besides debates about when the use of a non-consent approach is acceptable (based on the level of permissible risk), most of the focus in this area should be on the type and extent of required notifications.

5.2. Scope of Consent

Consents may be broad or narrow. A so-called "blanket consent" approach asks for consent to a wide category of uses and assumes that consent will cover all uses, unless one is specifically excluded. Blanket consent should be distinguished from broad or general consent that does not necessarily imply "blanket" consent to all uses. In agreement with legislation, broad consent refers to use in biomedical research, not to other kinds of uses, such as for forensic use or for use by immigration authorities. A blanket consent model has historically been relatively common and still exists in some contexts. For example, patients entering a health institution or agreeing to a procedure sometimes have a notation at the bottom of the general consent form allowing the use of leftover tissue in any way deemed appropriate by the institution. Extremely broad blanket consents are not generally viewed as valid exercises of autonomy and thus may not truly be considered to be "informed consent." At best, blanket consent may be viewed as a type of notification procedure, alerting individuals to the possible uses of their information. Neither the Federal human subjects research regulations nor the Privacy Rule permit extremely broad blanket consents. Some registries will have been created, with the use of a prior express legal permission from individuals, before the compliance date of the Privacy Rule, and additionally fall under an exemption to the human subjects research regulations; in these circumstances previously obtained broad blanket consent may be deemed sufficient.

The real issue related to the scope of consent is to what extent consent can and should authorize future unspecified uses. In other words, how broad a consent is permissible? The exercise of autonomy should include the ability to consent both to specific and to non-specific research participation. An individual who would like to give broad permission for the use of their data in any future registry (or for use in a particular registry, but include permission that the information may be shared with investigators for any future research query) is exercising a form of autonomy. As noted earlier, however, there are legal restrictions on the scope of these broad permissions. In addition, part of the issue is in determining whether a broad consent was truly informed. In the absence of specific details about the future uses, decisionmaking is necessarily less informed than if every future use is spelled out clearly. However, the ethical doctrine of informed consent does not require this level of detail. Moreover, requiring multiple consent dialogues may respect autonomy less than permitting broad consent if the individual does, in fact, wish to give broad permission and does not want continued re-contact. In some contexts, such as the donation of biological samples, broad consents are more acceptable (there is a long history of allowing unrestricted tissue donations). It has become common to provide a menu of options in a consent form for biological or genetic databanking. These allow participants to specify any constraints they would like to place on the of their samples, such as permitting use only for the specific study listed, or for all studies in a particular research areas (e.g., heart disease), or for any future study in any area. Details regarding whether and under what circumstances the participant would like to be recontacted may also be collected. By contrast, in other areas such as consent to participate in a clinical trial, broad consents (e.g., "I give consent to participate in any clinical trial") are insufficient on both ethical and regulatory grounds. For situations such as the use of medical information, the scope of a broad consent is less clear. The debates about the scope of consent are ongoing. While investigators should be aware of regulatory constraints, there are likely some broad consents that contain all of the ethically relevant elements.

5.3. Oversight and Community Consultation

Consent is only one aspect of the protections in place for human research participants. The other part involves IRB review and oversight. Other chapters discuss the oversight roles for IRBs and registry governance boards. While the idea of community consultation usually appears in the context of discussions on human subjects research consent, there is no simple community analog to individual consent. Consent requirements for research arise from the principle of autonomy, and there is no corresponding principle at the community level. Thus, concepts such as "community consent" or "community authorization" can be incoherent, in part because there is no unitary concept of a community. Communities may be defined on social, biological, religious, racial, cultural, or geographic grounds. Most people belong to multiple, sometimes overlapping, communities. Some of these communities may have a designated spokesperson, but this individual may not represent the interests of all members of the community (consider, for example, the complex relationship between the Pope and Catholics in the United States). Other communities have no clearly identified spokesperson. It is inappropriate to consider community consultation as a replacement for individual consent. Rather than view community involvement as an aspect of consent, it should be considered as part of oversight (and an analog of IRB review).[63] Community involvement in the design and oversight of a registry may be particularly important when the registry involves socially identifiable groups that have been subject to historic discrimination or when it involves sensitive genetic information. In some cases, community involvement can enhance participant understanding for consent and, in turn, increase individual participation.

6. Consent Guidance

Although general agreement has been reached about the required elements of informed consent for clinical research, this model may not be entirely applicable to informed consent for creation of and participation in registries. Risks to participants (and, when applicable, risks to groups and/or communities) should be balanced carefully with the public health benefits of registry development. The sensitive nature of information about participants and potential for broad data distribution highlight the importance of the informed consent process. Moving forward, informed consent elements and guidelines specific to registry research should be developed.

6.1. Special Considerations

Given the nature of registry research, some elements of informed consent should be given special consideration, including: the scope of the use of registry data, potential for recontact, withdrawal, and information regarding the electronic data security and management to be employed.

6.1.1. Scope of Use of Registry Data

Registries constitute a valuable resource since investigators often draw upon these to address questions extending far beyond those envisioned when the registries are first created. Therefore, informed consent for registry research that allows broad data sharing is optimal for promoting science. There may be instances, however, such as with respect to research on specific diseases (e.g., HIV/AIDS research), where more specific consent may be appropriate. Additional Federal level guidance on the appropriate scope of broad consent for future uses will be important. In the meantime, registry developers should not only provide clear parameters regarding the scope of use of registry data when first creating the registry, but should also develop a mechanism to consider how future, possibly unanticipated, requests for data access will be evaluated. The registry governance board can play an important role in this situation.

6.1.2. Recontact

Individuals should be informed how their data/samples will be used at the point of entry into the registry. Whether and how participants will be recontacted should be established at the outset and included in the consent form. Exceptions should be considered specifically where data/samples were made irretrievably anonymous, since recontact would then be impossible. It is important to inform registry participants that the anonymization of their data will make withdrawal from the registry impossible.

6.1.3. Withdrawal

Many issues governing withdrawing from a registry have been discussed in this chapter. Consensus needs to be developed regarding whether withdrawal should be presented as an option to participants in the initial consent, and, if it is an option, how withdrawal will be managed. While withdrawal from a traditional research study is a basic subject right, withdrawal of collected data, even from clinical trials, may be restricted. It is extremely important that registry creators develop initial rules and procedures for withdrawal and fully inform participants of these.

6.1.4. Electronic Data Security

Given the public concerns about electronic data security, participants in the registry should be clearly informed as to the physical security of their data and/or biospecimens, including methods of coding and removal of identifiers, encryption techniques, potential for cloud computing, and quality assurance policies. As well, participants should be informed about the process of releasing and transferring data to

future investigators as it relates to maintaining confidentiality. In some cases, this information will reassure participants, potentially increasing consent rates.

6.2. Proposed Consent Form Elements

The following is an outline of potential elements to consider when developing consent forms and engaging in consent dialogs for registry research. These elements were generated from the applicable HHS, FDA, and Privacy Rule requirements and include consent aspects particularly relevant to registry research. These are all issues that should be considered; there may be additional legal requirements (i.e., for a HIPAA authorization). The outline below should not be viewed as comprehensive or even applicable to all registries. Modifications will be appropriate for some registries, while others will follow a consent procedure similar to one used for traditional clinical trials. However, this outline provides a starting place for understanding the scope of informed consent for registry participation. It is important to note that the responsibility for obtaining and assuring appropriate informed consent rests on multiple parties, including sponsors, investigators, Protocol Review Committees (PRCs), and IRBs. Moreover, despite the multitude of elements listed below, every effort should be made to keep consent forms as short as possible and at approximately a 6th to 8th grade reading level.

1. A statement that the individual is being asked to take part in a registry (or a research study, if applicable)
    a. The name of the specific registry for which consent is being obtained
    b. An explanation of the purposes of the registry (why it was created, who will be included)
    c. The expected duration of participation
    d. A description of the procedures entailed
    e. The approximate number of subjects involved (if applicable)
2. A description of any foreseeable risks or inconveniences (specifically risks related to any potential breach of confidentiality related to the data being collected);
    a. When human genetic research is anticipated, information should include possible consequences of genetic testing (e.g., insurance risks, paternity determinations, potential risks to family and community) and other related confidentiality risks;
3. A description of the types of research that the repository will support, and any benefits to the subject or to others which may reasonably be expected;
    a. A statement about whether and how findings will be communicated to participants
4. A statement describing the extent to which confidentiality of data/biospecimens identifying the subject will be maintained (including a description of the operations of the repository--how data/specimens will be stored and managed);
    a. If applicable, a statement about whether registry result will be published
    b. A statement about the impact of participation on the subject's access to his/her medical records (e.g., that access may be limited until all work on the Registry is completed).
5. The conditions and requirements under which data and/or specimens will be shared with recipient investigators;
    a. If applicable, a description that the data/specimens will be broadly shared and may be used for future research that is not yet identified;
    b. The fact that the data/specimens may be transferred to other institutions and explanation of a data transfer security plan;
6. A description of when recontact might be necessary, and how recontact will be handled.

7. A statement of whether there are any costs to participation and/or any payment for participation
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
    a. The consequences of a subject's decision to withdraw from the research, including the possibility that the previously collected data will continue to be used, and procedures for orderly termination of participation by the subject.
9. Details on who to contact for answers to pertinent questions about the research and research subjects' rights.
10. As appropriate, any state-specific addendums

References for Chapter 8

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Case Examples for Chapter 8

Case Example 12. Issues with Obtaining Informed Consent

Description	The Registry of the Canadian Stroke Network (RCSN), now known as the Ontario Stroke Registry, is a registry of stroke patients in Canada. The registry, currently in Phase V, is a non-consent-based registry that collects detailed clinical data on the acute stroke event, from the onset of symptoms, emergency medical service transport, and emergency department care to hospital discharge status. The purposes of the registry are to monitor stroke care delivery, to evaluate the Ontario Stroke System, and to provide a rich clinical database for research.
Sponsor	Canadian Stroke Network, Networks of Centres of Excellence, and Ministry of Health and Long Term Care of Ontario
Year Started	2001
Year Ended	Ongoing
No. of Sites	154
No. of Patients	More than 60,000

Challenge

The registry began in 2001 with Phase I, in which data were gathered from 21 hospitals in Canada. All patients admitted to the hospital or seen in the emergency department with symptoms of acute stroke within 14 days of onset or transient ischemic attack (TIA), as well as those with acute in-hospital stroke, were included in this phase. Research nurse coordinators identified eligible patients through daily reviews of emergency and admission patient lists and approached these patients for consent. Informed patient consent was required for full data collection, linkages to administrative data, and 6-month followup interviews.

Despite the need for informed consent for full data collection, consent was obtained for only 39 percent of eligible patients. Subsequent analyses showed that patients who consented to participate were not representative of the overall stroke population, as they were less likely to have severe or fatal stroke, and also less likely to have minor stroke or TIA.

Phase II of the registry began in 2002, with 21 hospitals and 4 Ontario Telestroke sites. In this phase, all patients admitted to the hospital or seen in the emergency department with symptoms of acute stroke within 14 days of onset or TIA were included. Patients with in-hospital stroke were no longer recruited. In order to standardize workload across the country, a random sample of eligible patients was selected to be approached for consent for full data collection. Consent was obtained from 50 percent of eligible patients.

After obtaining consent of only 39 percent and 50 percent of patients in Phases I and II, the team realized that obtaining written patient consent for participation in the registry on a representative sample of stroke patients was impractical and costly. Patient enrollment threatened the viability and

generalizability of the stroke registry. The registry team published these findings in the *New England Journal of Medicine* in April 2004.

Proposed Solution

The registry team approached the Ontario Information and Privacy Commissioner to discuss a non-consent-based registry for Phase III. Because of these discussions, the registry was "prescribed" by the Privacy Commissioner under the Personal Health Information Protection Act, 2004, which allowed the registry to collect data legally on stroke patients without written consent.

Results

Phase III of the registry included all patients presenting to emergency departments of the 11 "Stroke Centres" in Ontario and 1 in Nova Scotia with a diagnosis of acute stroke or TIA within 14 days of onset. Nurse coordinators identified eligible patients through daily reviews of emergency and admission patient lists. Patients were identified prospectively, with retrospective chart review, without consent. No followup interviews were done. Because informed consent was not required, the data collected provided a representative sample of stroke patients seen at tertiary care centers in Canada, making the data more viable for use in research and in developing initiatives to improve quality of care. The registry has now expanded to include a population-based, province-wide audit of stroke care delivery on a 20-percent sample of patients from every acute care institution in Ontario.

Key Point

The impact of obtaining informed consent should be considered in developing a registry. Requiring that registries obtain the consent of patients with acute medical conditions such as stroke may result in limited selective participation, as it is not possible to obtain consent from all patients. For example, patients who die in the emergency department and patients who have brief hospital visits may be missed. Mechanisms such as obtaining a waiver of informed consent or using the approach outlined in this case may be alternatives.

For More Information

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Case Example 13. Operationalizing Informed Consent for Children

Description	TARGetKids! (Toronto Applied Research Group) is a prospective registry enrolling healthy children aged 0-5 years. The aim of the registry is to link early nutritional exposures to later health outcomes including obesity, micronutrient deficiency, and developmental outcomes.
Sponsor	University of Toronto
Year Started	2008
Year Ended	Ongoing

No. of Sites	7 primary care practices in Toronto, Canada
No. of Patients	4,287

Challenge

Research involving children faces unique challenges, including special requirements related to the informed consent process. TARGetKids! is a prospective patient registry enrolling healthy children aged 0-5 years. Patients are recruited at their annual well-child visits and followed up during subsequent annual well-child visits for ten years. Participation involves completion of age-specific questionnaires related to the child (nutrition, behavioural, and development), collection of anthropometric measurements, and collection of the child's blood sample (4-7 mL) by a trained pediatric phebotomist.

Consent for the registry is provided by one or both parents. By signing consent, parents also authorize the collection of their child's health card number to allow researchers to access the child's health records. Registry staff anticipated challenges in obtaining informed consent for these activities, particularly given the infrequency of contact with patients and the fact that blood sample collection is not part of normal clinical care during these annual visits. After reviewing the registry protocol, a research ethics board recommended that steps be taken to minimize coercion when recruiting and consenting patients.

Proposed Solution

Two weeks before a scheduled well-child visit for an eligible patient, the physician's office mails a short informational letter to the child's home. The purpose of the letter is to provide information about the registry and prepare parents for their contact with registry staff during the visit. By providing this information in advance, the letter minimizes the possibility that parents will feel coerced to consent to registry participation.

On the day of the visit, the child's parents are approached by a registry research assistant to provide consent for participation of their child in the registry. The research assistant explains what participation entails (i.e., completing questionnaires, collection of anthropometric measurements, and collection of a blood sample). If the parent spontaneously expresses that they wish to participate in the registry but don't wish to participate in one of these activities, they are given the option to opt out of one portion of the registry (e.g., blood collection) while still consenting for others (e.g., questionnaires and anthropometric measurements).

Results

The registry is now following 4,287 children aged 0 to 5 years from seven primary care practices in Toronto, Canada. The participation rate for the registry is 49% of all eligible children in the targeted practices (defined as children aged 0-5 years with a well-child appointment scheduled). The primary reasons parents decline to participate in the registry include lack of time to answer the questionnaire, no legal guardian accompanying the child, the need to discuss participation with spouse, and their child not feeling well that day.

Of consenting parents, about 50% consent to the registry blood sample. One possible reason parents choose to consent to the blood sample is that they see value in the test results (i.e., for iron or vitamin D deficiency) which are not standard of care for children in Canada. Although the informed consent form and registry staff do not emphasize this in an attempt to minimize coercion, parents may perceive it as an added benefit.

Key Point

Providing patients (and parents of pediatric patients) with information about the registry in advance can give them time to prepare questions and thoughtfully consider whether they wish to consent to participation. A flexible consent structure that allows patients to opt out of activities of a sensitive nature can reduce barriers to consent and participation.

For More Information

www.TARGetKids.ca

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Chapter 9. Protection of Registry Data from Litigation and Other Confidentiality Concerns for Providers, Manufacturers, and Health Plans

1. Background

As the cost of care delivered in the United States continues to grow at an unsustainable rate without parallel improvements in the quality of care,[1–8] healthcare policy experts and lawmakers are paying increasing attention to initiatives that measure and publicly report information about the performance of physicians, hospitals, and other health care providers as well as the services and procedures that are being delivered. They believe this is an important step to improving health care quality and controlling costs. For example, advancing quality improvement through greater access to and use of health information is a specific goal of the Patient Protection and Affordable Care Act (PPACA),[9] which includes a number of provisions to incentivize quality measurement, improvement, and reporting as well as enabling more informed decisionmaking by consumers and other stakeholders.

Critical to the success of these initiatives is the availability and accessibility of relevant administrative and clinical data. Data registries (or repositories) are often used to collect, process, maintain, and release relevant data for these purposes. For example, many professional associations and societies organized around provider specialties or specific diseases and conditions administer their own registries. Typically, these registries are used for a variety of patient safety and quality improvement activities including: matching patients with researchers, tracking the course of patients' care, tracking and identifying trends with medical errors or other patient safety issues, and tracking outcomes related to specific diseases or conditions or the effectiveness of specific treatments used to treat them. For example, the American College of Chest Physicians (ACCP) directs the ACCP Quality Improvement Registry, Evaluation and Education, or AQuIRE, intended to "assist the chest physician with meeting increasing demands placed upon them by the public, credentialing bodies, regulatory agencies, payers, and the institutions in which they practice."[10] Likewise, the American Orthopaedic Association spearheads the Own the Bone registry, designed to better coordinate patient care among a patient's providers, close the gaps associated with physician treatment recommendations, and alter patient and physician behaviors to reduce future incidence of bone fractures due to osteoporosis.[11] Quality improvement and clinical research registries are also organized by the American College of Rheumatology,[12] the American College of Radiology,[13] the Society for Thoracic Surgeons,[14] and the National Cardiovascular Data Registry.[15] Similarly, manufacturers and health plans often contribute data to or sponsor registries for quality improvement and clinical research, including identifying care delivery trends and whether or not a particular service, procedure, medical device, or pharmaceutical achieves the desired effect.

Administrative and clinical information submitted by or about providers, medical device and pharmaceutical manufacturers, and health plans and included in registries for research, quality measurement and improvement activities, and patient safety initiatives often includes sensitive patient, provider, and/or manufacturer or health plan-identifiable information. Release of this information in an identifiable or even non-identifiable manner may compromise the privacy of individual patients and providers involved as well as compromise sensitive financial, commercial, or proprietary manufacturer or health plan (e.g., benefit design, reimbursement) information. As more and more registries are developed and used for a variety of research (including comparative effectiveness research), quality improvement,

and patient safety programs, the range of information about patient safety, quality of patient care, performance, and other details about providers, medical devices, pharmaceuticals, and health plans grows. This information is incredibly useful to help providers better understand and improve the care they are delivering, help manufacturers refine and improve the devices and pharmaceuticals they are developing, and help patients make more informed choices about their providers and treatment options. However, this information is also desirable for use in litigation or other judicial or administrative proceedings to demonstrate that a certain level of care was adhered to or not or that a certain device or pharmaceutical works in a particular way.

Considerable attention has been directed towards ensuring the privacy and confidentiality of individually identifiable patient health information maintained in registries, particularly in regards to the requirements of The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.[16] As such, the privacy and confidentiality of individually identifiable patient health information is well established and recognized by Federal and state agencies, courts of laws, and others.

Significantly less attention has been directed towards the privacy and potentially proprietary nature of information supplied by or about providers, medical device and pharmaceutical manufacturers, and health plans. Often providers, manufacturers, and health plans are the best source of information to support the effectiveness of a registry whether it is used for research, quality improvement, patient safety initiatives, or other related activities. Even when they do not directly provide the information to a registry, they may be included in information provided by other sources (e.g., information submitted by a provider relating to a procedure performed on a patient involving Company Y's medical device). Numerous policy makers and researchers have noted the "chilling effect" that the lack of protection for the information provided may have on the willingness of providers, manufacturers, and health plans to provide (or be included as a direct or indirect subject of) relevant information to support research, quality improvement, and patient safety initiatives designed through registries. For example, commentary in the 2006 Journal of the American Medical Association reported that "wariness about liability exposure in the medical community may stymie public and private efforts."[17]

The 2000 Institute of Medicine (IOM) Report, "To Err is Human", explicitly identified this "wariness" as a significant issue that hampers voluntary reporting and collaborative efforts, including the free exchange of information, to identify medical errors and prevent their repetition. To address this issue, the IOM report recommended that Congress pass "legislation to extend peer review protections to data related to patient safety and quality improvement that are collected and analyzed by health care organizations for internal use or shared with others solely for purposes of improving safety and quality."[18] To date, however, no comprehensive Federal legislation has been passed. Thus, providers, manufacturers, and health plans must look to a variety of Federal and state laws that may offer protection from disclosure of information pursuant to a discovery request or other judicial or administrative proceedings.

2. Relevant Laws and Regulations: Variety of Sources, But Limited Protection

While no general Federal statutory privilege exists to protect information held in a registry submitted by or relating to providers, manufacturers, or health plans, there are a number of Federal laws that may provide protection from discovery or disclosure in judicial or administrative proceedings. In addition, most states have specific peer review or quality assurance laws that may provide additional protection as

well, but again in limited circumstances. This chapter will primarily focus on available Federal evidentiary protections, but will also address state specific protections. It concludes with an overview of mechanisms that may be used to protect information included in a registry during judicial or administrative proceedings. While registries may collect information from both within the U.S. and internationally, treatment of registries by international laws is outside the scope of this chapter.

2.1. Federal Laws

2.1.1. AHRQ Confidentiality Statute

All identifiable research data obtained by the Agency for Health Research and Quality (AHRQ) is protected by the agency's confidentiality statute.[19] The statute requires that data collected by AHRQ-sponsored entities that identifies individuals or establishments be used only for the purposes for which it is supplied. Any effort to determine the identity of a person in an AHRQ database, or to use the information for any purpose other than for research, analysis, and aggregate statistical reporting, violates the AHRQ confidentiality statute. Recipients of a data set are also prohibited from releasing, disclosing, publishing, or presenting any individually identifying information. Specifically, the statute provides:

> No information, if an establishment or person supplying the information or described in it is identifiable, obtained in the course of activities undertaken or supported under this subchapter may be used for any purpose other than the purpose for which it was supplied unless such establishment or person has consented (as determined under regulations of the Director) to its use for such other purpose. Such information may not be published or released in other form if the person who supplied the information or who is described in it is identifiable unless such person has consented (as determined under regulations of the Director) to its publication or release in other form.[19]

Concerns have been raised that this protection may be vulnerable if the information is disclosed to an outside entity such as a registry. However, AHRQ has interpreted this provision to protect all AHRQ-funded research from discovery requests, including discovery requests in the course of litigation. A memorandum from senior AHRQ attorney Susan Merewitz noted that "if individuals inside a health care institution are gathering identifiable medical error information as part of AHRQ-supported grant or contract research, and it is conveyed outside the institution, e.g., for analysis in an AHRQ-supported central databank, even if the reporters lost their protection against being subpoenaed to testify under State law, the Federal statute would cover and protect the identifiable information they acquired pursuant to AHRQ's statutory research authority."[20] While this memorandum is not binding on any court of law, and has yet to be introduced in a legal challenge, it clearly establishes AHRQ's protective position as it relates to any information collected under the auspices of an AHRQ supported project. Registries participating in AHRQ-sponsored activities would certainly be able to avail themselves of this protection and given the comments of Ms. Merewitz that protection may even extend to non-AHRQ activities where an AHRQ-sponsored entity holds the data as a repository or intermediary.

Importantly, this protection is limited to registries sponsored by AHRQ. Therefore, registries maintained by professional associations or other organizations that are not sponsored by or otherwise participating in an AHRQ-sponsored project would not be able to benefit from the protections afforded by the AHRQ confidentiality statute.

2.1.2. HHS Certificate of Confidentiality

The U.S. Department of Health and Human Services (HHS) may issue a "Certificate of Confidentiality" for any research project that collects personally identifiable, sensitive information and that has been approved by an Institutional Review Board (IRB). A Certificate protects an investigator, and others who have access to research records, to refuse from disclosing identifying information on research participants in any state or Federal judicial, administrative, or legislative proceeding. The Certificate may be used for biomedical, behavioral, clinical, or other types of research.

In the research arena, the National Institutes of Health (NIH) is the most common source for Certificates of Confidentiality. The NIH considers research to be sensitive if disclosing the information could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. According to NIH, examples of studies that may be considered sensitive include those collecting genetic information, information on subjects' psychological well being, information on sexually transmitted diseases or on subjects' sexual attitudes, preferences or practices, data on substance abuse or other illegal conduct, and studies where subjects may be involved in litigation related to exposures under study (i.e., breast implants, environmental or occupational exposures).[21]

The specific statutory language provides that:

> The Secretary [of the U.S. Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.[22]

There are four inherent shortcomings with the applicability of Certificates of Confidentiality to registries.[23] First, the protections only apply to the identity of research subjects, or to data that would allow the possible identification of such individuals. Thus, de-identified patient safety data is still potentially discoverable. Second, there are questions as to whether a Certificate applies to patients who have presumably not consented to becoming research subjects. Third, individual patients may be able to waive the Certificate protections as to their own information, which they presumably would do if they were plaintiffs in a malpractice lawsuit. Fourth, the protections only apply to research information that applies for, and is granted, a Certificate of Confidentiality. Therefore, the protections afforded by a Certificate of Confidentiality are limited and do not provide meaningful opportunities for registries that are not engaged in research and that have not applied for and been granted a Certificate.

2.1.3. The Patient Safety and Quality Improvement Act of 2005

The Patient Safety and Quality Improvement Act of 2005[24] creates a Federal privilege from discovery in connection with Federal or state judicial or administrative proceedings for certain information identified as patient safety work product. To claim the privilege, providers must create the patient safety work product and report it to a formally recognized patient safety organization (PSO) for aggregation and analysis. The term "patient safety work product" encompasses any data, reports, records, memoranda, analyses, or written or oral statements that meet one of two criteria: the materials "could improve patient

safety, health care quality, or health care outcomes" and are gathered by a provider to be reported and are reported to a PSO or are developed by a PSO to conduct patient safety activities; or the materials "identify or constitute the deliberations or analysis of, or fact of reporting to, a patient safety evaluation system."

Materials not gathered to be reported to the PSO and not actually transmitted to a PSO would not qualify for a privilege. The privilege specifically does not apply to medical records, billing and discharge information, or other records kept outside safety reporting systems. Furthermore, providers must comply with any state laws that require reporting of patient safety information. Thus, if a patient safety investigation references medical records, the records themselves do not become part of the work product eligible for protection.

Documents created, maintained, or developed separately from a patient safety evaluation system are excluded from the definition of patient safety work product. Thus, individual patient medical records, billing and discharge information, and any original patient or provider records are not considered work product and are thus not privileged. Indeed, these documents are not work product even if they, or copies of them, are entered into a patient safety evaluation system and/or provided to a PSO. In addition, information collected to comply with external reporting requirements is not work product.

The regulations identify several examples of information that must be reported and does not merit protection as work product, including state incident reporting, adverse drug event information reporting, records for compliance with health oversight agency requirements, reporting physician disciplinary actions to the National Practitioner Data Bank, and disclosures required under Medicare's conditions of participation. Thus, a significant amount of data remains outside the Patient Safety Work Product definition. This includes registry data that is not maintained by a PSO and used for specific patient safety work activities or is not identifiable. Therefore, the PSO statute and regulations provide no protection for registries acting outside the protected scope of the PSO arena.

2.1.4. Quality Improvement Organization Statute and Regulations

Quality Improvement Organizations (QIOs) are responsible for improving the effectiveness, efficiency, economy, and quality of services delivered to Medicare beneficiaries. The Centers for Medicare and Medicaid Services (CMS) contracts with one private, generally not-for-profit organization in every state, as well as the District of Columbia, Puerto Rico, and the U.S. Virgin Islands, to serve as that jurisdiction's QIO. QIO employees, consisting primarily of doctors and other health care professionals, are instructed to review medical care and assist beneficiaries with quality of care issues and complaints, as well as to implement improvements to the quality of care provided by providers.

The QIO statute provides that any data or information acquired by a QIO in its course of duties must be kept confidential and may not be disclosed to any person, except as it assists Federal and state agencies responsible for investigating cases of fraud and abuse, investigating cases involving risks to the public health, and to assist appropriate state agencies and national accreditation bodies responsible for the licensing or certification or providers or practitioners.[25]

Furthermore, the statute explicitly states that "no patient record in the possession of" a QIO may be subject to subpoena or discovery proceedings in a civil action.[26] Additionally, no document or other information produced by a QIO in connection with its deliberations may be subject to subpoena or discovery in any administrative or civil proceeding. However, a QIO shall provide, upon the request of a

practitioner or other person adversely affected by such deliberations, a summary of the QIO's findings and conclusions.

Additionally, QIO regulations state that quality review study information with a patient identifier is not subject to subpoena or discovery in a civil action, including administrative, judicial or arbitration proceedings.[27] This restriction, however, does not apply to HHS administrative subpoenas issued in the course of an audit or investigation of HHS programs, in the course of administrative hearings held under the Social Security Act, or to disclosures to the U.S. Government Accountability Office (GAO) as necessary to carry out its statutory responsibilities.

Similar to the PSQIA, the QIO statute and regulations provide protection only to information that has been collected by a QIO under contract with CMS to perform specific statutory functions. To the extent a QIO is the owner and operator of a registry used to perform required functions, the information included in the registry would be protected. However, this does not apply to the vast majority of registries currently in existence today.

2.1.5. HIPAA Privacy Rule

The privacy of individually identifiable health information is protected by the HIPAA Privacy Rule regulations.[28] The Privacy Rule only applies to "covered entities," which include health plans, health care clearinghouses, health care providers who conduct certain electronic health care transactions, and their business associates (e.g., contractor performing specific functions on their behalf).[29] The purpose of the Rule is to protect all "individually identifiable health information" held or transmitted by a covered entity or its business associate, in any form or media, whether electronic, paper, or oral. "Individually identifiable health information" is information, including demographic data, that relates to an individual's 1) past, present or future physical or mental health condition; 2) health care provisions; or 3) past, present, or future payment for health care provisions. The information must also identify the individual or reasonably lead to individual identification, and usually consists of common identifiers, such as name, address, birth date, and Social Security Number.[30] The Privacy Rule refers to this information as "protected health information" (PHI).

The Privacy Rule includes a liberal exception for disclosure of PHI in the course of any judicial or administrative proceeding in response to an order of a court or administrative tribunal.[31] Absent a court order, a covered entity also may respond to a subpoena or discovery request from a party to the proceeding if the covered entity obtains either: 1) satisfactory assurances that reasonable efforts have been made to give the individual whose information has been requested notice of the request; or 2) satisfactory assurances that the party seeking such information has made reasonable efforts to secure a protective order that will guard the confidentiality of the information.

In meeting the first test, a covered entity is considered to have received satisfactory assurances from the party seeking the information if that party demonstrates that it has made a good faith effort (such as by sending a notice to the individual's last known address) to provide written notice to the individual whose information is the subject of the request, that the written notice included sufficient information about the proceeding to permit the individual to raise an objection, and that the time for the individual to raise objections to the court or administrative tribunal has elapsed and no objections were filed or any objections filed by the individual have been resolved.

A "qualified protective order" means an order of a court or of an administrative tribunal or a stipulation that: 1) prohibits the parties from using or disclosing the protected health information for any purpose other than the litigation or proceeding for which the records are requested; and 2) requires the return to the covered entity or destruction of the protected health information (including all copies made) at the end of the litigation or proceeding. Satisfactory assurances of reasonable efforts to secure a qualified protective order are a statement and documentation that the parties to the dispute have agreed to a protective order and that it has been submitted to the court or administrative tribunal with jurisdiction, or that the party seeking the protected health information has requested a qualified protective order from such court or tribunal.

Importantly, the protections of HIPAA will only apply if a registry is considered a covered entity or the business associate of a covered entity. This may be the case if the registry is considered a "healthcare clearinghouse" if its function is to "process or facilitate the processing of health information received from another entity in a nonstandard format or containing nonstandard data content into standard data elements."[32] The more likely scenario is that the registry is acting as the business associate of a covered entity (e.g., collecting and processing information on behalf of provider(s) and/or health plan(s)). However, even if the registry is considered a covered entity or business associate, the minimal protections of HIPAA in the case of disclosure pursuant to a court order, subpoena or discovery request only apply to PHI. To the extent the requested information does not include PHI (e.g., the information is considered to be de-identified), HIPAA does not protect information about providers, manufacturers or any other entities. Therefore, in the case of providers, manufacturers, and health plans seeking protection of de-identified information specific to them or their products, HIPAA does not shield them from discovery requests in litigation or any other court proceedings.

2.1.6. Privacy Act of 1974

The Privacy Act of 1974[33] protects information about individuals, such as patients and providers, held by or collected by the Federal government that can be retrieved by personal identifiers such as name, social security number, or other identifying number or symbol. The Privacy Act authorizes a Federal agency to release individually identifiable information to identified persons or to their designees with written consent or pursuant to one of twelve exemptions for disclosure.[34] These exemptions include disclosure to Federal agency employees, the Census Bureau, the National Archives and Records Administration, other government entities for civil and criminal law enforcement purposes, the Comptroller General, Congress or its committees, and a consumer reporting agency.[35] Additional exemptions include disclosures for statistical research, disclosures required by Freedom of Information Act, disclosures in response to emergency circumstances, and importantly for purposes of this chapter, disclosures pursuant to a court order.

Unless the Federal government maintains the registry, the Privacy Act of 1974 offers no protection from discovery for litigation or related court proceedings. Furthermore, even if the Federal government maintains the registry, the Privacy Act specifically allows for the release of identifiable information about individuals without their written consent pursuant to a court order. This could include information not only about individual patients, but also individual providers (e.g., individual practitioners).

2.1.7. Freedom of Information Act

Enacted by Congress in 1966, and expanded in 1996 to cover electronic records,[36] the United States Freedom of Information Act (FOIA)[37] generally provides that any person has the right to obtain access to information contained in the records of Federal agencies, unless such information is specifically protected from disclosure by FOIA. With a goal of ensuring an informed citizenry, capable of holding the government accountable, FOIA effectively establishes a statutory right of public access to executive branch information, requiring that virtually every record held by a Federal agency be provided to individuals upon request.[38] Information that is subject to FOIA is likely to be disclosable pursuant to a discovery request or other court proceeding. However, FOIA does have limited exemptions and exclusions to the broad disclosure requirements. The most relevant exemptions for purposes of protection of registry information are Exemption Four, Exemption Six, and Exemption Three.

Exemption Four protects "trade secrets and commercial or financial information obtained from a person and privileged or confidential."[39] Importantly, however, it is not a mandatory bar to disclosure, but rather limits an agency's obligation to disclose specified information. "Trade secrets" are defined as commercially valuable plans or formulas for producing trade commodities to which has been invested substantial effort or innovation.[40] In the case of registries that contain information supplied by or about providers, medical device or pharmaceutical manufacturers, and health plans, it is likely that only the pharmaceutical and medical device manufacturers and health plans would have information that could be considered "trade secrets." Furthermore, information contributed to a registry by manufacturers is more likely to be considered "commercial" or "financial." For example, in Public Citizen Health Research Group v. Food & Drug Administration,[41] the court found that "because documentation of the health and safety experience of their products will be instrumental in gaining market approval for their products it seems clear that the manufacturers … have a commercial interest in the requested information."[42]

Exemption 6 states that information about individuals in "personnel and medical files and similar files" can be withheld from disclosure by Federal agencies when the disclosure of such information "would constitute a clearly unwarranted invasion of personal privacy."[43] In order to warrant protection under Exemption 6, the information at issue must first meet the threshold requirement of falling into one of three categories – personnel files, medical files and similar files. The Supreme Court found that Congress intended these categories to be interpreted broadly and to protect information that "applies to a particular individual."[44] Once it has been established that the information meets this threshold, the focus shifts to whether the disclosure of such information would be an unwarranted invasion of privacy. This requires balancing the public's right to disclosure of the information against the individual's right to privacy. After determining that a protectable privacy interest exists, the public's interest in disclosure of the information will be weighed against the individual's privacy interest in not disclosing the information.

The landmark Supreme Court decision in *United States Department of Justice v. Reporters Committee for Freedom of the Press*[45] governs how privacy interests under Exemption 6 are determined and balanced with public interest in the information. First, the Court clarified that a substantial privacy interest may exist in information that has already been released to the public at some point. Second, the Court held that the identity of the individual or party requesting the information may not be taken into consideration when determining if information should be released and "has no bearing on the merits of his or her FOIA request."[46] When considering the public interest in disclosing the information, the Court ruled that the determination should be based on the nature of the requested information and its relationship to the public

interest generally, and not solely the purpose for which the request is made. Finally, the Court narrowed the scope of the public interest to the kind of interest to information that will "shed light on an agency's performance of its statutory duties."[47]

It is important to note, however, Exemption Six only protects information that identifies the individual in question. Thus, while patient records included in a registry are likely to be protected, if identifying information is removed, the information is no longer protected under Exemption Six. The most common types of information protected under Exemption Six are age, home address, Social Security number, medical information about individuals participating in clinical research trials, claims files, and other personal information held by CMS.[48]

Exemption Three protects information if it is "specifically exempted from disclosure by statute, provided that such statute (A) requires that the matters be withheld from the public in such a manner as to leave no discretion on the issue, or (B) establishes particular criteria for withholding or refers to particular types of matters to be withheld."[49] An example of a statute that may prevent disclosure or discovery of information contained in a registry under FOIA Exemption Three would be the Patient Safety Quality Improvement Act of 2005 (discussed above) if the information met the PSQIA requirements.

2.1.8. Federal Trade Secrets Act

The Federal Trade Secrets Act[50] imposes fines or imprisonment on any Federal employee who discloses any information that relates to trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses or expenditures of any person or corporation. The Act applies only to public disclosures, and does not reach internal agency use of the data.

There is no private right of action under the statute; however, the Administrative Procedure Act may create a right of action to prevent a violation of the Trade Secrets Act or review a decision to disclose information.[51] Similar to Exemption Four under FOIA, the Federal Trade Secrets Act may protect proprietary information, however, only to the extent that is held by the Federal government and disclosed publicly (e.g., may not reach information disclosed pursuant to a protection order as part of a discovery proceeding.).

2.1.9. Federal Rules of Evidence and Civil Procedure

Federal legal rules of evidence and civil procedure may place limits on what information may be discoverable or otherwise used in a court proceeding. For example, Rule 401 of the Federal Rules of Evidence defines "relevant evidence" as evidence having any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence."[52] Rule 403 narrows the scope of Rule 401 stating "although relevant, evidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury…"[53] Often of the most relevance to information contained in registries is the bar in Rule 404 against "evidence of other … acts … to prove the character of a person in order to show action in conformity therewith."[54] This may apply in instances where information is sought from a registry to show evidence of similar medical outcomes.

Turning to Civil Procedure, Rule 26(b)(2)(C)(iii) of the Federal Rules of Civil Procedure provides that a court may limit discovery if "the burden or expense of the proposed discovery outweighs its likely

benefit, considering … the importance of the discovery in resolving the issues."[55] Rule 26(c) also allows parties from whom discovery is sought to move for a protective order.[56] Rule 45(c) protects individuals from unduly burdensome or expensive subpoenas. Specifically, 45(c) states, "a party or attorney responsible for issuing and serving a subpoena must take reasonable steps to avoid imposing undue burden or expense on a person subject to the subpoena. The issuing court must enforce this duty and impose an appropriate sanction — which may include lost earnings and reasonable attorney's fees — on a party or attorney who fails to comply."[57] It is left to the discretion of the court in each case to determine whether the facts and circumstances merit quashing a specific subpoena.

While these Federal rules of evidence and civil procedure may offer protection against discovery of registry information in certain situations, their application is left entirely to the discretion of the particular court in which the case is heard. Thus, the case law is mixed with some courts allowing discovery and others not depending on their application of a balancing test of the need for confidentiality vs. hardship to the party seeking discovery. For example, in Andrews v. Eli Lilly & Co., Inc., E.R. Squibb & Sons and Rexall Drug Company,[58] Squibb sought production of data from a University of Chicago registry that included information about a disease related to a products liability action against Squibb. The University of Chicago claimed that the contents of the registry were privileged and confidential. In balancing the privacy interests of the registry against the need for the information, the court stated, "the balance … tips in favor" of the registry.[59] "Squibb's need for the information is speculative and uncertain. Its essentially private interest in defending itself is outweighed by the compelling social interest in preventing harm to the Registry and the vital work it conducts."[60] The court, however, did allow discovery of information contained in the registry related to the plaintiffs. Squibb appealed and in Deitchman v. E.R. Squibb & Sons,[61] the appellate court noted that the privilege was not "absolute" and remanded the case back to the lower court to determine the best way to provide information from the registry while preserving confidentiality.[62] In a second hand smoke case, Wolpin v. Phillip Morris Inc.,[63] the court ordered disclosure of data from a statewide tumor registry from a study by the University of South California and California Department of Health despite objections that the data was protected by state and Federal privacy laws. The court held that the confidentiality interest was outweighed by the need for the information in the lawsuit, but did require patient names to be removed prior to release.

2.1.10. Patient Protection and Affordable Care Act: Release of Medicare Claims Data for Provider Performance Measurement and Reporting

Section 10332 of PPACA requires the Secretary to make Medicare claims data available to qualified entities for the evaluation of provider performance on measures of quality, efficiency, effectiveness, and resource use.[64] The data are standardized extracts of claims data under parts A, B, and D for items and services furnished for one or more specified geographic areas and time periods requested by a qualified entity. The qualified entities will be required to pay a fee to obtain the data and must submit to the Secretary of HHS a description of the methodologies that will be used to evaluate the performance of providers and suppliers.

All subsequent reports published by a qualifying entity must include an understandable description of the measures, risk adjustment methods, physician attribution methods, other applicable methods, data specifications and limitations, and the sponsors, so that consumers, providers of services and suppliers, health plans, researchers, and other stakeholders can assess such reports. In addition, the reports must be made available to any provider or supplier identified in the report, with an opportunity to appeal and

correct any errors. Finally, the reports may only include information on a provider or supplier in an aggregate form as determined appropriate by the Secretary.

The Secretary may not make claims data available to a qualified entity unless the entity agrees to release the information on the evaluation of performance of providers of services and suppliers. Section 10332 requires that data released to a qualified entity shall not be subject to discovery or admission as evidence in judicial or administrative proceedings without consent of the applicable provider or supplier.[65]

While limited in application to Medicare claims data provided to qualified entities, this provision is a significant recognition by Congress of concerns related to the "chilling effect" the fear of disclosure has on provider, supplier (including manufacturer), and health plan participation in quality measurement, improvement and reporting programs. By shielding this information from discovery or admission as evidence without consent, Congress has explicitly protected and incentivized the activities of qualified entities, including the development of registries to support their performance measurement and reporting efforts.

2.2. State Laws

2.1.1. State Surveillance Laws

To encourage practitioner participation in state surveillance registries, many states have passed legislation providing immunity from civil and criminal penalties that may arise in conjunction with such reports. Most states protect providers from any liability that may result from a disease report unless the provider acted with some level of negligence or malicious intent.[66] Fewer states provide complete immunity for reporting disease cases to a registry, with no distinction made for negligent or intentionally malicious reports.[67] Additionally, other states provide immunity only for certain causes of action related to the information reported, or protect from civil liability only.[68] However, case law implicating such state harbors is sparse, with most cases affording immunity for health care professionals who report sexually transmitted diseases discovered in minors in potential child abuse cases.[69]

2.1.2. State Peer Review and Quality Assurance Laws

Presently, all 50 states have enacted statutes to protect the confidentiality of the peer review process. Most statutes offer a blanket protection for all accounts, records and conclusions of the review process from being introduced into evidence during any court proceeding.[70] Without such protection, providers and hospitals may be less inclined to truthfully monitor their peers, evaluate the quality of care that is provided to patients, or to adequately prevent or correct for adverse events.

A few states also have passed legislation specifically protecting information collected for quality improvement and other related purposes. These "safe harbor" laws protect a broader set of information beyond the traditional peer review process, including collection by organizations outside the scope of an internal peer review board or committee. For example, in Minnesota, information relating to patient care collected by a nonprofit organization for purposes of "evaluating and improving the quality of health care" or "reviewing the safety, quality or cost of health care services" provided to health plan enrollees "shall not be disclosed to anyone … and shall not be subject to subpoena or discovery."[71] The Virginia Patient Safety Act protects the collection of patient safety data by "statewide or local associations" representing licensed health care providers. It treats the information collected as "privileged communications which may not be disclosed or obtained by legal discovery proceedings unless a circuit

court, after a hearing and for good cause arising from extraordinary circumstances being shown, orders the disclosure of such proceedings, minutes, records, reports, or communications."[72] Similarly, the Illinois Medical Studies Act protects all information "used in the course of internal quality control or of medical study for the purpose of reducing morbidity or mortality, or for improving patient care or increasing organ and tissue donation." Such information is "privileged, strictly confidential, and shall be used only for medical research, increasing organ and tissue donation, [or] the evaluation and improvement of quality care."[73] It is not "admissible as evidence, nor discoverable in any action of any kind in any court or before any tribunal, board, agency or person."[74]

However, it is important to note that the peer review privilege and other state-based protections are often not recognized in Federal cases outside the jurisdiction of state law. Federal courts have been resistant to establish a Federal peer review or other privilege, and often subordinate the state peer review privileges in favor of other interests. For instance, the 11th Circuit Court of Appeals recently declined to recognize such a privilege during a Federal civil rights discrimination case, ordering the discovery of peer review documents.[75] Similar outcomes have been reached in many other Federal courts, including cases deciding Federal antitrust[76] and wrongful termination claims.[77]

2.3. Practical Considerations

As described above, Federal and state law currently do not provide any consistent or comprehensive protection from disclosure pursuant to discovery or other judicial or administrative proceedings of information submitted by (or that is related to) providers, medical device or pharmaceutical manufacturers, or health plans to registries. This leaves registries that are operating outside of the government-sponsored programs described above, their participants and subjects, vulnerable to discovery requests ranging from preliminary fact-finding requests to court orders. As the IOM noted this can have a "chilling effect" on willingness of providers to participate. The same is also true for manufacturers and health plans that similarly may be both a source of information as well as the subject of information included in a registry. Beyond concern for the privacy and confidentiality of the information, the costs and burden associated with discovery or other requests can be substantial often taking months or years as the litigation process unfolds. These costs may include not only costs related to challenging the request, but also data production, including costs for redaction (particularly where patient identifiable information is involved), and the costs of legal representation.

There are several steps that registries as well as their participants can take to reduce their vulnerability to disclosure requests. As described above, there are several Federal programs that protect information collected for specific patient safety and quality improvement purposes. (See Case Example 15.) If registries qualify for or are funded through these programs, the information collected and maintained would automatically be entitled to protection from discovery or other judicial or administrative proceedings. While not always possible or practical given their goals or priorities, registries should consider whether or not participation in any of these programs would be appropriate.

To the extent participation in one of these Federal programs is not possible, registries and their participants should consider formation in a state that provides broader protection for information collected beyond the peer review process (e.g., VA, MN, or IL). Furthermore, registries and their participants should clearly articulate their roles and responsibilities, including how discovery or other requests will be handled. Registries should develop specific policies and procedures that will guide their response to any

such requests and should ensure that all participants are familiar with the policies and procedures. (See Case Examples 14 and 16.) For example, registries might stipulate that they will direct all disclosure requests to the original source of the information where possible. Where information held within a registry has been aggregated and analyzed such that it is significantly modified from its original state, the registry will notify the original data sources prior to compliance with any discovery request and give them the opportunity to object.

In the event a registry is compelled to release information pursuant to a court order or other judicial or administrative order, registries may request certain information be redacted or a protective order issued. A court protective order can stipulate who can see the information, who has access to the information, and rules for destruction or return of the data. Similarly, a registry may request that the information be "sealed" by the court so that they are not made public. These types of actions have historically been used to protect patient-identifiable information held in registries, however, they may be similarly applied to confidential or proprietary information related to providers, manufacturers or health plans.

3. Summary

As more and more attention is focused to the development and implementation of quality improvement activities, including those tied to new payment models, availability and accessibility of underlying clinical and administrative data that registries can provide to support these efforts will be increasingly important. This emphasis will be further strengthened as the new Patient Centered Outcomes Research Institute authorized to support efforts to generate comparative effectiveness research begins its work. Given this heightened interest in registries as a data source, the issue of protection of registry data from disclosure pursuant to a discovery request or other judicial or administrative proceedings will be increasingly important. Registry sponsors may be able to address concerns from potential participants about data protection by considering these issues during the registry development stage. In particular, providers, manufacturers, and health plans that are developing a registry or considering participation in a registry should look to the variety of Federal and state laws described here that may offer protection and should consider the practical steps outlined above to reduce their vulnerability to disclosure requests.

References for Chapter 9

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[67] *See, e.g.* N.C. GEN STAT. §130A-142 (2010) (a provider who reports "shall be immune from any civil or criminal liability that might otherwise be incurred or imposed as a result of making that report").
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Case Examples for Chapter 9

Case Example 14. Handling Discovery Requests for Registry Data

Description	The ICD Registry captures the characteristics, treatments, and outcomes of patients receiving implantable cardioverter defibrillators (ICDs). Participation in the registry is required by a coverage decision of the Centers for Medicare and Medicaid Services (CMS). In addition to CMS reporting, participating hospitals may use their data to monitor and improve the outcomes and management of ICD patients through implementation of evidence-based clinical guidelines.
Sponsor	American College of Cardiology Foundation (ACCF)
Year Started	2005
Year Ended	Ongoing
No. of Sites	Over 1600 laboratories
No. of Patients	Over 800,000 procedures

Challenge

Prior to its launch, the ICD Registry received significant attention from the public and researchers because of the CMS coverage decision. The registry sponsors anticipated that the registry would generate interest from outside entities seeking to discover registry data, particularly those investigating potential fraud (e.g., the Office of the Inspector General), those desiring to use registry data in malpractice lawsuits (e.g., litigation attorneys), and those seeking to corroborate information published in the peer-reviewed literature (e.g., media). Driven by these concerns, the sponsor and registry staff sought to address this anticipated issue proactively.

Proposed Solution

Registry staff implemented a series of processes and procedures to assist all parties involved in handling a discovery request. In coordination with general counsel and outside counsel, internal policies were drafted and provisions were written into contracts with participating sites that explained how discovery requests would be handled by registry staff, the process of responding to a discovery request from an attorney, the process of cooperating with the Office of Inspector General during an audit or investigation, and best practices for protecting registry data from discovery. This language prepared sites for these procedures should they ever occur, made them aware of their options in these situations (i.e., cooperate with or dispute the request), and clarified the level of protection that the registry offered for their data.

Standard operating procedures were implemented to train staff to recognize a discovery request and subpoena and to describe the actions that should be taken to appropriately triage and respond to discovery requests for registry data (e.g., site support staff direct such requests to the registry compliance office). More in-depth staff training was provided, including role play scenarios in which staff tested their skills and confidence through simulated discovery requests.

Results

Since 2005, the registry has received five different requests for registry data, from sources as varied as attorneys, the Office of the Inspector General, and members of the press. The requests are managed in a consistent, documented way, regardless of whether the registry first receives these requests via site support staff or other venues. The registry maintains a relationship with the ACCF general counsel so that questions about future requests can be promptly resolved.

Key Point

Registries can take proactive steps to manage discovery requests for their data. Appropriate steps may include confidentiality provisions in contracts with sites and targeted training for all levels of registry staff.

For More Information

http://www.ncdr.com/webncdr/ICD/Default.aspx

Case Example 15. Meeting the Confidentiality and Quality Improvement Needs of Providers through a Patient Safety Organization

Description	The Pediatric Peri-Operative Cardiac Arrest (POCA) Registry investigated the incidence, causes, and outcomes of cardiac arrest among children undergoing anesthesia. The Wake Up Safe (WuS) Initiative is a quality improvement initiative and registered Patient Safety Organization (PSO) that aims to improve processes of care and outcomes for children undergoing anesthesia.
Sponsor	American Society of Anesthesiologists and the University of Washington (POCA); Society for Pediatric Anesthesia (WuS)
Year Started	1994 (POCA) and 2008 (WuS)
Year Ended	2005 (POCA) and ongoing (WuS)
No. of Sites	58-79 (POCA) and 18 (WuS)
No. of Patients	374 events from >3.5 million anesthetics (POCA) and 518,000 anesthetic records (WuS)

Challenge

Children undergoing anesthesia have an increased risk of cardiac arrest compared to adults. Although various factors associated with this increased risk had been identified, the causes of these arrests and their outcomes were not well understood. The POCA Registry was formed in 1994 by the American Society of Anesthesiologists and the University of Washington to collect detailed case reports of cardiac arrests during anesthesia in pediatric patients. These case reports were submitted by institutions anonymously, in order to protect the participating institutions and the registry from legal risk of disclosure.

In 2000, the registry analyzed the first 4 years of data (1994-1997) and found that the incidence of anesthesia-related cardiac arrest was 1.4 per 10,000 anesthetics, with a mortality rate of 26%. The most common causes were medication-related and cardiovascular, with cardiovascular depression from halothane (a commonly-used anesthetic in children) accounting for two-thirds of medication-related cardiac arrests. This suggested a target for preventive strategies, including avoidance of halothane when a new agent (sevoflurane) was available. In 2007, the registry published an update on its findings, comparing cardiac arrests from 1998-2004 to the cardiac arrests in the initial report. This report found fewer medication-related cardiac arrests (associated with a decline in use of halothane) and more arrests with undetermined causation.

Despite these promising findings, the pediatric anesthesiology community sought a more comprehensive approach to quality care improvement. The registry only collected data on pediatric cardiac arrest, and not on any other outcomes, processes, or quality of care indicators. In addition, because data was submitted anonymously to the registry, benchmarking at the institution level was not possible. There were also concerns about the protection of registry data. The registry was housed in the state of Washington, which had legal protections in place to protect quality improvement data from legal discovery – however, not all states had these same protections in place.

Proposed Solution

In 2005, the POCA Steering Committee decided to halt case collection as compliance with reporting had declined. While the registry had contributed much to understanding of anesthesia-related cardiac arrest in children, it was felt that further data collection using the same methodology was unlikely to produce additional insights.

In 2007, the Society for Pediatric Anesthesia (SPA) began garnering support to form the Wake Up Safe Initiative, a new quality improvement initiative for pediatric anesthesiology. As institutions joined, they signed participation agreements with the SPA that were intended to address intellectual property issues, but evolved as each hospital had its own concerns about privacy, protection, and anonymity in reporting. By 2008, ten institutions had signed on to participate in the initiative. The same year, the Patient Safety and Quality Improvement Act of 2005 came into effect, which provides Federal legal protections to information reported by providers to a patient safety organization (PSO). WuS applied for and was granted PSO status in 2008.

Results

The WuS initiative captures a broad range of outcomes, and individual institutions are not identifiable. Anesthetic records for pediatric patients are extracted from the administrative billing systems of member hospitals and provided to the registry on a quarterly basis. This provides background data on which to base incidence calculations. Individual event case reports are provided to the registry on an ad hoc basis, as they occur. To date, 18 member hospitals have contributed 518,000 anesthetic records and 450 event case reports to the registry.

As a PSO, the registry provides more complete protections for the providers contributing data. These include limits on the use of registry data in civil, administrative, and some criminal proceedings, and provisions for monetary penalties for violations of confidentiality or privilege protections.

Key Point

Registries, particularly those that collect sensitive information on provider performance, should consider taking advantage of the legal protections that are available to patient registries. Official designation as a patient safety organization (PSO) offers broader Federal protections that individual states may not be able to offer. This may provide an incentive for participation, especially for registries that collect sensitive information on performance or quality of care.

For More Information

www.wakeupsafe.org

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Case Example 16. Protections Available to Registry Data from Institutional Review Boards and Academic Institutions

Description	The Postoperative Visual Loss (POVL) Registry consists of anonymous case reports of blindness after non-ophthalmologic surgery. Its goal is to identify patient and clinical factors associated with this complication.
Sponsor	American Society of Anesthesiologists
Year Started	1999
Year Ended	Ongoing
No. of Sites	Not applicable
No. of Patients	191

Challenge

Blindness after non-eye surgery is a rare but devastating complication. Blindness due to ischemic optic neuropathy after spine surgery appeared to be increasing in the 1990s and its causation was unknown. Its rarity created difficulty in studying causative factors.

Proposed Solution

A registry was created to collect detailed case reports of blindness after non-ophthalmologic surgery, and included data pertinent to all known theories of causation of postoperative visual loss. Due to the potential for malpractice litigation when postoperative blindness occurs, case reports were submitted without patient, provider, or institutional identifiers. It was hoped that anonymity of case reports would protect the registry from legal discovery and encourage case report submission by healthcare providers. The registry was housed at the University of Washington and its institutional review board (IRB) approved these confidentiality procedures.

Results

In spite of these procedures to protect confidentiality of case reports, numerous requests for release of registry data were submitted by plaintiff attorneys. Following university policy, all requests were referred to the office of public information. All such public information requests were denied based on the institutional review board approved confidentiality procedures.

One public information request for registry data was appealed through the court system. A registry investigator was serving as a defense expert in a malpractice lawsuit, basing her testimony on published registry results. The plaintiff requested raw registry data. When this request was denied by the university, the plaintiff sought to strike the investigator's testimony because she would not produce the raw registry data underlying the publication that formed the basis of her testimony. The trial court determined that the raw registry data was discoverable because the defense expert considered such data in forming her opinion. The university supported an appeal to the state supreme court in order to support institutional protections of research data. The state supreme court ruled that the author could testify based on the published results and release of the underlying data was not required.

Key Point

It is critical to consider protection of sensitive registry data from legal discovery. When developing and implementing registries, consider protections that may be available through IRB study approval and academic institutions. Seek guidance from IRBs or university counsel, as needed.

For More Information

http://www.cobar.org/opinions/opinion.cfm?opinionid=7861&courtid=2

Lee LA, et al. The American Society of Anesthesiologists Postoperative Visual Loss Registry: Analysis of 93 spine surgery cases with postoperative visual loss. Anesthesiology 105:652-9, 2006

The Postoperative Visual Loss Study Group: Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. Anesthesiology 116:15-24, 2012.

Section III. Operating Registries

Chapter 10. Recruiting and Retaining Participants in the Registry

1. Introduction

Recruitment and retention of participants are essential elements in the design and operation of a registry. Registries are often intended to be representative of a certain population of patients and reflective of the practices of certain providers and geographic areas. The problems commonly associated with clinical studies—such as difficulties with patient enrollment, losses to followup, and certain sites contributing the majority of patients—can also have profound consequences on validity of registry data. When registry patients are not representative of the target population, the value of the results is diminished. For example, in regard to policy determinations, the enrolled sites or providers must be representative of the types of sites and providers to which the policy determination would apply in order for the results of the registry to be generalizable. Differences in how effectively sites enroll or follow patients can skew results and overly reflect the sites with the most data. This oversampling within a particular site or location must also be considered in sample size calculations. If the sample size of a key unit of analysis (patient, provider, or institution) is not sufficient to detect a clinically important difference, the validity of the entire registry is weakened. (See Chapters 3 and 13.)

Well-planned strategies for enrollment and retention are critical to avoiding these biases that may threaten registry validity. Because registries typically operate with limited resources and with voluntary rather than mandatory participation, it is particularly important to balance the burdens and rewards of participation in the registry. The term "voluntary" in this context is intended to mean that participation in the registry by either providers or patients is not mandated (e.g., by the U.S. Food and Drug Administration), nor is participation required as a necessary condition for a patient to gain access to a health care product or for a provider to be eligible for payment for a health care service.

Registries that are not voluntary have different drivers for participation. In general, the burden of participation should be kept as low as possible, while the relative rewards, particularly nonmonetary rewards, should be maximized. As described in Chapters 2 and 4, minimizing burden typically starts with focusing on the key goals of the registry.

Building participation incentives into a registry should also be included in the planning phase. A broad range of incentives—spanning a spectrum from participation in a community of researchers, to access to useful data or quality improvement benefits, to continuing medical education, to public recognition or certification, to payments or access to patients—have been used in registries. The ability to offer certain incentives (e.g., linking payment for a service to participation in a registry or access to patients) may be available only to certain registry developers (e.g., payers, licensing entities). Many registries incorporate multiple types of incentives, even when they pay for participation. Monetary incentives (e.g., from payers or sponsors) are very helpful in recruiting sites. However, because the payments should not exceed fair market value for work performed, registries cannot solely rely on these incentives. A number of nonmandated registries have achieved success in recruitment and retention by providing a combination of

ethical incentives that are tailored to and aligned with the specific groups of sites, providers, and patients that are asked to participate. (See Case Examples 17, 18, 19, 20.)

2. Recruitment

Depending on the purpose of a registry, recruitment may occur at any of three levels: facility (e.g., hospital, practice, and pharmacy), provider, or patient. While frequently recruitment at these levels is part of a design to accrue a sufficient number of patients for sample size purposes, such as for a safety registry, the individual levels may also constitute potential units of analysis (and as such, may further affect sample size, as discussed in Chapter 3.8). As an example, a registry focused on systems of care that is examining both hospital system processes and patient outcomes might need to consider characteristics of the individual patients, the providers, and/or the places where they practice (i.e., clusters). If the question is about the practices of orthopedic surgeons in the United States, the registry will be strengthened by describing the number and characteristics (e.g., age, gender, and geographic distribution) of U.S. orthopedic surgeons, perhaps by citing membership data from the American Academy of Orthopedic Surgeons. This will allow documentation of the similarities and differences in the characteristics of the surgeons participating in the registry compared with the target population. (See Chapter 3.7.)

2.1. Hospital Recruitment

A hospital or health system may choose to participate in a patient registry for many reasons, including the research interest of a particular investigator or champion, the ability of the hospital to achieve other goals through the registry (such as requirements for reimbursement, certification, or recognition), or the general interest of the particular institution in the disease area (e.g., specialty hospitals). Increasingly, external mandates to document compliance with practice standards provide an incentive for hospitals to participate in registries that collect and report mandatory hospital performance or quality-of-care data. For example, a number of registries allow hospitals to document their performance to meet the Joint Commission requirements for hospital accreditation.[1] Hospitals in the United States must submit these data to maintain accreditation. Therefore, hospital administrators may be willing to supply the staff time to collect these data without the need for any additional financial incentives from the registry sponsor, provided that registry participation allows the hospital to meet external quality-of-care mandates. In other cases, participation in a quality monitoring or health system surveillance registry may be required by payers or governments for reimbursement, differential payments, or patient referrals under various programs, ranging from the Centers for Medicare & Medicaid Services (CMS) public reporting initiative, to centers of excellence programs, to pay-for-performance programs. One particular example, CMS's Coverage With Evidence Development (CED) programs,[2] which may require participation in a registry for the center or provider to qualify for payment for a procedure, can have a dramatic impact on registry participation. Registry participation requirements have existed for implantable cardioverter defibrillators (ICDs) for preventing sudden cardiac death in heart failure, bariatric surgery, positron emission tomography (PET) scan use in cancer, and others, and have rapidly resulted in high participation rates for registries meeting the program requirements.

The presence of quality assurance departments in U.S. hospitals provides an infrastructure for participation in many hospital-based registries and therefore a natural target for recruiting. However, hospital size, service line (e.g., disease-specific centers), and competing activities may limit institutional interest. The American Hospital Association database provides a valuable resource for identifying

hospitals by key characteristics, including hospital ownership, number of beds, and the presence of an intensive care unit.

Table 11 summarizes the key factors for successful hospital recruitment and lists specific methods that might be used for recruiting hospitals. While programs need not incorporate all of these characteristics or use all of these methods, successful programs typically incorporate several.

Table 11. Hospital Recruitment

Keys to hospital recruitment	• The condition being studied satisfies one of the hospital's quality assurance mandates. • Sufficient funds, data, or other benefits will be realized to justify the effort required to participate. • The confidentiality of the hospital's performance data is ensured, except to the extent that the hospital elects to report it. • Clinically relevant, credible, timely, actionable self-assessment data—ideally, data that are risk adjusted and benchmarked—are provided back to the hospital to help it identify opportunities for enhancing patient care outcomes. • High-profile hospitals (regional or national) are participating in the registry. • Burden is minimized. • Participation assists the hospital in meeting coverage and reimbursement mandates, gaining recognition as a center of excellence, or meeting requirements for pay-for- performance initiatives.
Methods of hospital recruitment	• Identify eligible hospitals from the American Hospital Association database. • Utilize stakeholder representatives to identify potentially interested hospitals. • Enroll hospitals through physicians who work there and are interested in the registry. • Use invitation letters or calls to directors of quality assurance or the chief of the clinical department that is responsible for the condition targeted by the registry. • Ask physician members of an advisory board (if applicable) to network with their colleagues in other hospitals. • Reach out to physicians or hospital administrators through relevant professional societies or hospital associations. • Leverage mandates by external stakeholders, including third-party payers, health plans, or government agencies.

2.2. Physician Recruitment

There are many reasons why a physician practice may or may not choose to participate in a voluntary registry. As with hospitals, these reasons can include the research interests of the physician and the ability of the practice to achieve other goals through the registry (such as reimbursement or recognition). When deciding to participate, physicians often focus on several concerns:

- *Relevance*: Does the registry have meaning for the practice and patients?

- *Trust*: Are the registry leaders credible? Are the goals clearly stated?
- *Risks*: Will confidentiality be maintained? Are patient records secure?
- *Effort*: Will the amount of effort expended be fairly compensated?
- *Disruption*: Will participation disrupt workflow of the staff?
- *Value*: What benefits will be derived from participation? Will it improve the care provided? Will it enhance the evidence base for future practice?

Physicians who manage only a few patients per year with the disease that is the subject of the registry are less likely to be interested in enrolling their patients than physicians who see many such patients—unless the disease is rare or extremely rare, in which case the registry may be of great interest.

Because most registries are voluntary and physicians in nonacademic practice settings may have less infrastructure and staff available to enroll their patients, recruitment of representative physicians is a major challenge for registries that aim to compare physician practices across a full spectrum of practice settings. In general, community-based physicians are less well equipped than hospital-based or academic physicians to collect data for research studies because they work in busy practices that are geared to routine clinical care rather than research. To increase recruitment of nonacademic physicians, it can be helpful to clearly explain the purpose and objectives of the registry; how registry data will be used; and, specifically, that individual results will not be shared (except at the direction of the physician) or published, and that registry outcomes data will be released only in large aggregates that protect the identities of individual hospitals, physicians, and patients. In addition, any incentives should be clearly articulated.

Table 12 describes the key factors for successful physician recruitment and lists several methods that might be used for recruiting physicians.

Table 12. Physician Recruitment

Keys to physician recruitment	• The condition being studied is part of the physician's specialty. • The registry is a valuable scientific endeavor. • The registry is led by respected physician opinion leaders. • The registry is endorsed by leading medical, government, or patient advocacy organization(s). • The effort needed to recruit patients and collect and submit data is perceived as reasonable. • Useful practice pattern and/or outcome data are provided. • The registry meets other physician data needs, such as maintenance of certification requirements, credentialing requirements, or quality-based, differential, reimbursement payment programs (pay-for-performance).
Methods of physician recruitment	• Purchase mailing lists from physician specialty organizations. • Ask opinion leaders in the field to suggest interested colleagues. • Partner with local and national medical societies or large physician hospital organizations. • Use stakeholder representatives to identify interested physicians. • Recruit and raise awareness at conferences. • Advertise using e-mail and the Web. • Register in the Registry of Patient Registries (RoPR) to increase awareness. • Leverage practice-based research networks.

2.3. Vetting Potential Hospital and Physician Participants

Once potential hospital or physician participants have been identified, it is important to vet them to ensure that the registry is gathering the appropriate mix of data. Issues to consider when vetting potential participants include:

- Representativeness.
- Hospital characteristics (e.g., bed size, geographic location).
- Physician characteristics (e.g., specialty training).
- Practice setting (health maintenance organization [HMO], private practice).
- Ability to recruit patients.
- Volume of target cases.
- Internal resources.
- Availability of a study coordinator.
- Availability of Internet connectivity for studies with electronic data capture.
- Prior performance, including reliability and accuracy of data entry.

2.4. Patient Recruitment

Patients may be recruited based on the judgment of the physician who provides their care; the diagnosis of a disease; receipt of a procedure, operation, device, or pharmaceutical; membership in a health insurance plan; or being a member of a group of individuals who have a particular exposure. Recruitment of patients by the physician who is providing their care is one of the most successful strategies. The direct involvement in and support of the registry by their personal physicians is an important factor for patients. Since registries should not modify the usual care that physicians provide to their patients, there should be little or no conflict between their role of physician and that of participant in the registry. (See Chapter 7.) In addition, patients may see participation in the registry as an opportunity to increase their communication with their clinician. Another incentive for many patients is the feeling that they are contributing to the knowledge base of sometimes poorly understood and undertreated conditions.

Recruitment of patients presents different challenges, depending on the nature of the condition being studied. In general, patient recruitment plans should address the following questions:

- Does the plan understand the needs and interests of potential participants?
- Does the plan address patient recruitment issues and procedural challenges, including informed consent and explanation of risks?
- What are the patient retention goals? What is a reasonable followup period? What is a reasonable followup rate? When does reduced retention compromise validity?
- What, if any, patient incentives are offered, including different types of incentives and the ethical, legal, or study validity issues to be considered with patient incentives?
- What are the costs of patient recruitment and retention?

Table 13 summarizes the key factors for patient recruitment and lists several specific methods that might be used for recruiting patients, grouped by the basic categories of patients at the time of recruitment.

Table 13. Patient Recruitment

Keys to patient recruitment	• Recruit through a physician who is caring for the patient. • Communicate to the patient that registry participation may help to improve care for all future patients with the target condition. • Write all patient materials (brochures, consent forms) in a manner that is easily understandable by the lay public. • Keep the survey forms short and simple. • Provide incentives. These can be nonmonetary, such as functions relevant to the patient's care (reports) or community (newsletters, portals). In some cases, monetary incentives can be offered if approved by the institutional review board. • Actively plan how to include minorities or other populations of interest.
Methods of patient recruitment	• Noninstitutionalized residents of the general U.S. population: o Recruit via letter survey, telephone, or e-mail. o Recruit during well-patient visits to outpatient clinics. o Recruit via patient advocacy and support groups, health information Web sites, etc. o Register in the Registry of Patient Registries (RoPR) to increase awareness. • Outpatients attending the clinic of a physician who is participating in the registry: o Recruit through the patient's physician. o Recruit via brochures placed in physician's office. • Hospital inpatients who are hospitalized for treatment of a condition that is the subject of the registry: o Recruit through the patient's physician. o Recruit through hospitalists or consultant specialists. o Recruit through a hospital research coordinator. • Residents of nursing homes and similar long-term care facilities: o Establish a relationship with the nursing home and staff.

2.5. Partnerships to Facilitate Recruitment

Many agencies/organizations can assist in the recruitment of physicians and patients. These partners may have access to patients or their families and physicians who treat the condition, and they may lend credibility to the effort. These agencies/organizations include:

- Government agencies.
- Physician professional associations or State medical associations.
- Certifying boards (e.g., American Board of Neurological Surgeons).
- Patient advocacy groups (e.g., Muscular Dystrophy Association).
- Nonprofit foundations (e.g., Robert Wood Johnson Foundation).
- Industry (e.g., pharmaceutical companies).
- HMOs and other third-party insurance providers.

2.6. Procedural Considerations Related To Recruitment

When developing a recruitment plan for a registry, consideration should be given to the procedural concerns that may be factored into potential participants' decisions. These concerns include the roles and

responsibilities of each party, the need and process for obtaining institutional review board (IRB) approval, and the management of patient and provider confidentiality.

The contract between registry sites and the sponsor or coordinating center should clearly state the roles and responsibilities of the participants, the registry-coordinating center, and the sponsor. If monetary remuneration is being offered, the data entry requirements that need to be fulfilled before payments are made should be stated. It is often helpful to explain to sites the concept of fair market value. There is no specific formula (such as whether to separate startup payments from per-patient payments), but total remuneration must reflect work effort for the specific registry. Some individual factors, ranging from location to specialty, may have a bearing on fair market value. It is also important to spell out which entity will have ownership of the data and how the data will be used.

The contract should clearly explain the registry policy regarding any necessary approvals. If review by an IRB is required, generic templates can be offered to participants to assist them in obtaining ethical and IRB approval. Because the costs of obtaining IRB approval are often substantial, it is essential that the contract with the participants clearly indicates which party is responsible for bearing this cost. If the registry developer believes that IRB or privacy board review or approval is not required or may be waived, then a clear rationale should be provided to the prospective participants (see Case Example 54). As discussed in Chapter 7, the research purpose of the registry, the status of the developer, whether the Common Rule applies to the particular site, and the extent to which the data are individually identifiable largely determine applicable regulatory requirements. For example, for registries limited to certain purposes, such as quality improvement, institutions may not require IRB approval.[3]

Patient privacy and participant confidentiality should be addressed in the registry materials. Methods of ensuring patient privacy need to be clearly elucidated in all registry-related documentation. Case report forms and patient logs must be designed to minimize patient identification (such as by transmitting limited data sets rather than more identifiable information, if such information is not required to meet a registry objective).

The intended management of the confidentiality of participating providers should be explained in the contract. Mechanisms for protecting provider confidentiality, including Certificates of Confidentiality and Patient Safety Organizations, are discussed in Chapters 7 and 9. If third-party or public reporting is an intended component of the registry, the specific data to be shared, the level of the disclosure (e.g. hospital and/or physician level) and the permitted receiving entities need to be articulated and the control mechanisms explained.

3. Retention

3.1. Providers

Once hospitals and physicians are recruited to participate in a registry, retaining them becomes a key to success. All of the factors identified as important for recruitment are important for retention as well. A critical factor in retention is delivery on promises made during recruitment (e.g., that the burden of participation is low). By carefully pilot testing all aspects of the registry prior to full recruitment, there is less likelihood that problems will arise that threaten the registry's reputation. Registries with an advisory board or steering committee can use this resource to help with retention. A visible and independent advisory board adds transparency and credibility, sets appropriate expectations among its peers on what to

expect from a registry (e.g., compared with a clinical trial), ensures that the burden of the registry is minimized (or at least never outweighs its value to participants), and maintains the relevance and currency of the registry for the investigators. Ideally, advisory board members serve as ambassadors for the program. The level of credibility, engagement, practicality, and enthusiasm of the advisory board can significantly affect provider recruitment and retention. For example, an advisory board whose clinical members are not themselves participating in the registry will have greater difficulty than a board with participating members in addressing the concerns of participating practices that invariably arise over the course of the registry. Patient retention efforts may also be supported by the inclusion of patients or patient advocacy organization representatives on the advisory board. These representatives can provide feedback to the board on patient issues or concerns about the registry and facilitate communication about the registry's purpose and value to their peers or members.

Throughout the duration of the registry, communication from the data coordinating center and the advisors, as well as community building, are important for strong retention. Early and continued engagement of the site champions or principal investigators is very important. Some registries utilize periodic face-to-face meetings of principal investigators from participating sites. When this approach is not economically feasible, well-planned online meetings can serve the same purpose.

Visibility of the registry at relevant national meetings can help maintain clinician awareness and sense of community, and regular demonstration of its value through presentations and publications reinforces the credibility of the registry to its participants. As the dataset grows, so too does the value of the registry for all participants, and regular updates on the registry growth can be important. Finally, enhancing site value through nonfinancial rewards can be particularly useful in retention, and the registry should continually seek to bring value to the participants in creative and useful ways.

Participation retention tools include:

- Web sites.
- Newsletters.
- Telephone helplines.
- Instruction manuals.
- Training meetings.
- Site audit/retraining visits.
- Customer satisfaction/opinion surveys.
- Regular data reports to stakeholders.
- Presentations at conferences.
- Regular reports to registry participants on registry growth and publications.
- Ability of participating physicians to publish based on registry data (depending on the data access policy of the registry).

3.2. Patients

Retaining patients as active participants in registries with longitudinal followup is an ongoing challenge. Many factors need to be considered in developing a retention plan, including how long the patient is likely to return to the enrolling site. Patients enrolled in a primary care practice for a chronic illness can likely be followed in that practice for some time, although there should be a plan for how the registry will

(or will not) address the issue of patients who transfer to unenrolled practices. Patients enrolled in a hospital at discharge or through a specialist who does not follow the patient long term require different solutions. A range of options exists. They include enlisting site staff to reach out to patients beyond their standard interactions,[4] following patients directly through a central patient management center,[5] and linking to other data sources (e.g., National Death Index, claims data) to obtain key long-term outcomes data on patients who are lost to followup. Retention plans, including contingencies, should be considered during registry planning, as they may require additional permissions (e.g., for direct contact) or data elements (e.g., for linkage). Maintaining ethical incentives for patient participation (ranging from newsletters to payments) is important for some registries (e.g., those that collect patient-reported outcomes data). Beyond planning for how to retain patients in a registry, it is important to track actual vs. expected followup rates over time and to respond if rates are not meeting expectations. The resources available for patient retention efforts should also be clear. Followup rates can often be improved with more efforts, such as more attempts to contact the patient, but these efforts add costs and, at some level, will yield diminishing returns.

4. Pitfalls in Recruitment and Retention

Pitfalls abound in recruitment and retention. The most important of these pitfalls is the risk of selection bias. Targeting hospital- or academic-based physicians to the exclusion of community-based physicians is tempting because the former are often more accessible and are frequently more open to involvement in, and more experienced in, research projects. Similarly, targeting high-volume practices or centers will improve efficiency of patient enrollment, but may not yield an adequately representative sample of care practices. If an advisory board or committee is used to help design the registry and aid in recruitment, there may be a tendency for advisors to recruit known colleagues or to target disease experts, when a wider range of participants may be necessary to provide the appropriate data to meet the research goals. Including representatives from the range of anticipated site types on the advisory board can be helpful.

Even with an appropriate mix of physician participants in a registry, biases in patient recruitment may still occur. For example, older and more seriously ill patients may be excluded because of challenges in enrollment and followup or poorer outcomes. From the outset, physicians involved in recruitment efforts need to be aware of the potential for bias, and they must understand the importance of adhering to well-delineated inclusion and exclusion criteria. They must also adhere to the registry's enrollment strategy, which is typically designed to reduce this bias (e.g., consecutive or randomized enrollment). In addition, overly demanding data collection requirements can affect retention. The schedule should be designed to obtain relevant data in a timely fashion without overtaxing the resources of patients and providers. It is also important to consider approaches that will distinguish patients who are lost to followup from those who have missing data for other reasons (such as a patient who missed a visit but is still in the registry).

Another major pitfall is confusing terminology. This can be a major problem when the registry is international. When designing training materials, instruction manuals, and questionnaires, it is critical that the language and terminology are clear and concise. Materials that are translated into other languages must undergo strict quality assurance measures to ensure that terms are translated properly (e.g., back translation).

5. International Considerations

While many general principles are similar for participant enrollment and retention in other parts of the world, there are many different customs or regulations regarding contract language, requirements for ethics committee or other submissions, informed consent, and allowable approaches to patient retention. Registries that extend to other countries should consult national and local regulations in those countries.

References for Chapter 10

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Case Examples for Chapter 10

Case Example 17. Building Value as a Means to Recruit Hospitals

Description	Get With The Guidelines® is the flagship program for in-hospital quality improvement of the American Heart Association (AHA) and American Stroke Association (ASA). The program uses the experience of the AHA and ASA to ensure that the care that hospitals provide for heart failure, stroke, and resuscitation is aligned with the latest evidence-based guidelines.
Sponsor	American Heart Association and American Stroke Association
Year Started	2000
Year Ended	Ongoing
No. of Sites	3,150
No. of Patients	3,174,462 patients and 4,253,461 patient records in Get With The Guidelines-Inpatient (Stroke, HF, and Resuscitation)

Challenge

Recruiting hospitals for registries or quality improvement (QI) programs can be arduous. Human and financial capital is constrained. Accreditation and reimbursement programs, such as those of The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations, or JCAHO) and Centers for Medicare & Medicaid Services (CMS), contend for the same valuable human and financial capital. As a result, in the absence of specific benefits, many hospitals defer the data collection and report utilization required for successful QI execution.

Like most registries and QI programs, the sponsor's program faced barriers to data entry. Unlike other registries, Get With The Guidelines offered no reimbursements for data entry and entered a market characterized by significant competition. The registry team wanted to motivate resource-strapped hospitals to consistently and proactively enter data and analyze improvement.

Proposed Solution

The registry team began by listening to the hospitals through indepth interviews designed to understand the motivations and deterrents underlying behavior. Interviews were conducted with hospital decisionmakers at all levels (nurses, QI professionals, administrators/chief executive officers, and physicians).

Based on the research findings, the team developed strategies that differentiated and built value for the program. Some of the more noteworthy strategies included the following:

- Systems were designed to allow data transmission from and to Joint Commission and CMS vendors, enabling hospitals to reduce the burden of duplicate data entry while still participating in other programs.

- A new tagline, Turning Guidelines into Lifelines[SM], linked the brand's value proposition to the brand name and logo. Key messages for each target audience were included in marketing communications.
- A newly designed national recognition program motivated participation and advancement, and received the attention of hospital decisionmakers.
- Return-on-investment studies for the program demonstrated the value of participation.

Product innovations/enhancements created additional incentives to participate. Immediate point-of-care flags highlighted variances from guidelines. Benchmarking filters/reports empowered decisionmakers to benchmark performance with national averages and data from similar institutions. Customizable notes explaining diseases, tests, and medications can be sent to both the referring physician and the patient.

Results

By providing a mix of innovative nonfinancial incentives, the program increased both enrollment and advancement by about one-third in 12 months. Currently, 3,150 hospitals participate in the program. The database includes 4,253,461 patient records and is considered by many to be the most robust database for heart failure, stroke, and resuscitation. In 2004, the program received the Innovation in Prevention Award from the Department of Health and Human Services.

Key Point

Nonfinancial incentives that meet the needs of decisionmakers can assist in recruitment of sites. When creating such incentives, consider both tangible and nontangible benefits.

For More Information

www.heart.org/quality

Case Example 18. Using Registry Tools to Recruit Sites

Description	The objective of the OPTIMIZE- HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry was to improve quality of care and promote evidence-based therapies in heart failure. The registry provided a comprehensive process-of-care improvement program and gathered data that allowed hospitals to track their improvement over time.
Sponsor	GlaxoSmithKline
Year Started	2003
Year Ended	2005
No. of Sites	270
No. of Patients	More than 50,000

Challenge

The registry was designed to help hospitals improve care for patients hospitalized with heart failure. The objective was to accelerate the adoption of evidence-based guidelines and increase the use of the guideline-recommended therapies, thereby improving both short-term and long-term clinical outcomes for heart failure patients.

Proposed Solution

To increase compliance with guidelines, the registry team promoted the implementation of a process-of-care improvement component and the use of comprehensive patient education materials. They combined these materials into a hospital toolkit, which included evidence-based practice algorithms, critical pathways, standardized orders, discharge checklists, pocket cards, and chart stickers. The toolkit also included algorithms and dosing guides for the guideline-recommended therapies and a comprehensive set of patient education materials. The team engaged the steering committee in designing the toolkit to ensure that the materials reflected both the guideline-recommended interventions and the practical aspects of hospital processes.

In addition to the toolkit, the registry offered point-of-care tools, such as referral notes and patient letters, that could be customized for each patient based on data entered into the registry. The registry also included real-time performance reports that hospitals could use to assess their improvement on a set of standardized measures based on the guidelines.

Results

The hospital toolkit was a key component of the registry's marketing campaign. Hospitals could view the toolkit at recruitment meetings, but they did not receive their own copy until they joined the program. The toolkit gained credibility among hospitals because its creators included some of the most prominent members of the heart failure community. Hospitals also actively used the reports to track their improvement over time and identify areas for additional work. Overall, the registry recruited 270 hospitals and met its patient accrual goal six months ahead of schedule.

Key Point

Nonfinancial incentives, such as patient education materials, toolkits, and reports, can encourage sites to join a registry. Incentives that also add value for the site by improving their processes or providing materials that they use frequently can aid retention.

For More Information

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Case Example 19. Using a Scientific Advisory Board To Support Investigator Research Projects

Description	The National LymphoCare Study (NLCS) is a large, prospective, disease-based registry in the area of follicular lymphoma in the United States. There are a number of open clinical questions related to follicular lymphoma treatment, including whether anthracyclines should be used early in the course of disease and whether there is a group of patients for whom observation (as opposed to active treatment) is the best choice, given the indolent nature of the disease. The registry follows patients for up to 10 years, and specific outcomes of interest include overall response rate, progression-free survival, time to subsequent therapy, and overall survival for common front-line and subsequent therapeutic strategies.
Sponsor	Genentech, Inc., and Biogen Idec, Inc.
Year Started	2004
Year Ended	Ongoing
No. of Sites	250 community and academic sites
No. of Patients	Over 2,700

Challenge

The National LymphoCare Study includes a large number of community-based sites in addition to many academic sites. Many of the principal investigators at the community-based sites are interested in using the registry data to answer clinical questions, but they do not have sufficient research experience to design a research question, conduct data analysis, and share the results with the scientific community. One aim of the registry sponsors and scientific advisory board (SAB) is to facilitate research among the community investigators, both to increase interest in the registry and to increase the scope of research questions addressed using registry data.

Proposed Solution

The registry sponsors and the SAB developed a plan to allow investigators at enrolling sites to propose a question of interest; work with an SAB member, clinical scientists, epidemiologists, and biostatisticians to develop an analysis plan to answer the question; and present findings at scientific meetings. The plan was implemented in 2007, when the registry issued a call for research proposals to all participating investigators. The proposal outlined the types of data that were available at that point (e.g., descriptive data on demographics, initial treatments, etc.). Several community-based investigators sent in proposals, which the SAB then reviewed. The SAB selected the proposals that it felt were most appropriate for the available data and that answered the most valuable questions from a clinical standpoint.

The community investigator for each selected proposal was then paired with a member of the SAB to further develop the research question. This process included conference calls and e-mails to refine the question and the high-level analytic plan. Once the high-level analytic plan was ready, the investigator and the SAB member submitted the proposal and analytic plan to the registry sponsor. The sponsor

provided support for analytic design and biostatistics. The investigator, in consultation with the SAB member, developed an abstract based on the results. Abstracts were reviewed by the full SAB before being submitted for presentation.

Results

In 2007, a community-based investigator project developed through this process was accepted for abstract presentation at the annual American Society of Hematology (ASH) meeting. In 2009, a community-based investigator and a fellow at an academic institution developed abstracts that have been submitted for presentation at the annual ASH meeting.

With outcomes data now available in the registry, registry sponsors plan to issue calls for proposals twice per year, with the goal of generating abstracts for the annual ASH meeting and the annual American Society of Clinical Oncology (ASCO) meeting. To date, the research program has been well received by community-based investigators, who have the opportunity to author their own research projects with mentoring from an experienced advisor. The SAB has also been enthusiastic about working with community-based physicians on research methodology and adding to the scientific knowledge about this disease.

Key Point

Community-based investigators who participate in a registry may be interested in pursuing research opportunities but may not have all of the necessary resources or expertise. By utilizing an engaged advisory board, it is possible to provide investigators with research opportunities, resulting in more publications and presentations based on registry data, and potentially more engaged investigators.

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Case Example 20. Identifying and Addressing Recruitment and Retention Barriers in an Ongoing Registry

Description	Tracking Operations and Outcomes for Plastic Surgeons (TOPS) is a national registry of plastic surgery procedures and outcomes used to track and assess 30-day post-operative outcomes.
Sponsor	American Society of Plastic Surgeons (ASPS)
Year Started	2002
Year Ended	Ongoing
No. of Sites	425-450 annually
No. of Patients	611,682 complete cases and 1,094,268 plastic surgery procedures

Challenge

TOPS was initially launched in 2002 as a program designed to provide ASPS member plastic surgeons with a mechanism to track demographic, procedural, and outcomes information to help physicians benchmark and evaluate their practice. The registry uses an electronic data capture interface to collect common demographic, risk factor, procedural, and 30-day outcome data elements, which allow registry users to evaluate outcomes based on patient comorbidities and risk factors and track the rate and type of surgical incidences that could occur postoperatively. The registry has become an integral part of ASPS efforts and is utilized in many of the society's key initiatives, including developing evidence-based practice parameters, monitoring clinical outcomes and emerging trends, supporting research and educational programs, and compilation of the National Clearinghouse Plastic Surgery Statistics.

A majority of the registry participants contribute data annually. However, due to the voluntary nature of the registry, the registry also includes "one-time" users. Since 2002, over 1600 ASPS members have participated in the registry at any given time, leaving a large number of ASPS members choosing not to participate at all, and some ASPS members who choose to stop participating or participate sporadically. In order to encourage broad and continued participation from society members, the society sought to fully understand the needs of its members and develop strategies to retain and recruit participants for the ongoing registry.

Proposed Solution

To improve the program's value to member surgeons, the ASPS regularly evaluates member and organization needs to make upgrades and improve the registry. The ASPS surveyed its society membership in 2008 and 2012 to better understand reasons for both continued participation and lack of use. Survey results indicated that earning credits towards continuing medical education (CME), society-awarded patient safety credits, and contributing to important scientific endeavors were strong reasons for continued participation. In addition, individual physician practices perceived value in the registry's ability to track patients' outcomes over time and benchmark practice data against other practices in the registry. Many non-users reported the willingness to participate if the registry supported integration with their practice's electronic medical records (EMR) system. Other reasons for non-participation

included perceived limited usefulness of data collection to physician practice and site-based barriers such as insufficient resources.

Results

Based on the survey feedback, the ASPS elected to increase functionality to make the registry more relevant to members. Updates to the registry were made in 2007, 2009 and 2011, and included the introduction of credentialing reports, enhanced benchmarking reports, collection of patient-reported outcomes (PRO), and enhanced data entry and querying reporting functions. The credentialing reports allow registry users to review their individual patient data by facility, with options to filter by medical record number, name, date range, procedure type, and outcome. The existing benchmarking reports were enhanced, allowing users to benchmark their individual data against aggregate registry data; customizations were also added, allowing users to filter by time period and procedure type. The registry also began electronically collecting PRO data from breast augmentation and reconstruction patients using the BREAST-Q© questionnaire; the PRO data supports metrics for documenting clinical performance appraisal and improvement based on the patients' responses. Users can develop PRO reports and create dynamic customized graphs and charts in order to assess patient satisfaction across PRO domains, such as satisfaction with outcome, psychosocial well-being, and satisfaction with care. In response to member requests, the upgrades also included new functionality to support data transfer from EMR and practice management programs to ease data entry burden on sites.

Key Point

Within an ongoing, voluntary registry, retaining and recruiting participants requires maintaining relevance to users. Surveys or other methods of collecting feedback from registry participants and potential participants can be useful tools for discovering recruitment or retention barriers and identifying potential improvements to maintain relevance.

For More Information

http://www.plasticsurgery.org/for-medical-professionals/surgeon-community/tops.html

Chapter 11. Data Collection and Quality Assurance

1. Introduction

This chapter focuses on data collection procedures and quality assurance principles for patient registries. Data management—the integrated system for collecting, cleaning, storing, monitoring, reviewing, and reporting on registry data—determines the utility of the data for meeting the goals of the registry. Quality assurance, on the other hand, aims to assure that the data were, in fact, collected in accordance with these procedures and that the data stored in the registry database meet the requisite standards of quality, which are generally defined based on the intended purposes. In this chapter, the term *registry coordinating activities* is used to refer to the centralized procedures performed for a registry and the term *registry coordinating center* refers to the entity or entities performing these procedures and overseeing the registry activities at the site and patient levels.

Because the range of registry purposes can be broad, a similar range of data collection procedures may be acceptable, but only certain methodologies may be suitable for particular purposes. Furthermore, certain end users of the data may require that data collection or validation be performed in accordance with their own guidelines or standards. For example, a registry that collects data electronically and intends for those data to be used by the U.S. Food and Drug Administration (FDA) should meet the systems validation requirements of that end user of the data, such as Title 21 of the Code of Federal Regulations Part 11 (21 CFR Part 11). Such requirements may have a substantial effect on the registry procedures. Similarly, registries may be subject to specific processes depending on the type of data collected, the types of authorization obtained, and the applicable governmental regulations.

Requirements for data collection and quality assurance should be defined during the registry inception and creation phases. Certain requirements may have significant cost implications, and these should be assessed on a cost-to-benefit basis in the context of the intended purposes of the registry. This chapter describes a broad range of centralized and distributed data collection and quality assurance activities that are currently in use or expected to become more commonly used in patient registries.

2. Data Collection

2.1. Database Requirements and Case Report Forms

Chapter 1 defined key characteristics of patient registries for evaluating patient outcomes. They include specific and consistent data definitions for collecting data elements in a uniform manner for every patient. As in randomized controlled trials, the case report form (CRF) is the paradigm for the data structure of the registry. A CRF is a formatted listing of data elements that can be presented in paper or electronic formats. Those data elements and data entry options in a CRF are represented in the database schema of the registry by patient-level variables. Defining the registry CRFs and corresponding database schema are the first steps in data collection for a registry. Chapter 4 describes the selection of data elements for a registry.

Two related documents should also be considered part of the database specification: the data dictionary (including data definitions and parameters) and the data validation rules, also known as queries or edit checks. The data dictionary and definitions describe both the data elements and how those data elements

are interpreted. The data dictionary contains a detailed description of each variable used by the registry, including the source of the variable, coding information if used, and normal ranges if relevant. For example, the term "current smoker" should be defined as to whether "smoker" refers to tobacco or other substances and whether "current" refers to active or within a recent time period. Several cardiovascular registries, such as the Get With The Guidelines® Coronary Artery Disease[1] program define "current smoker" as someone who smoked tobacco within the last year.

Data validation rules refer to the logical checks on data entered into the database against predefined rules for either value ranges (e.g., systolic blood pressure less than 300 mmHg) or logical consistency with respect to other data fields for the same patient; these are described more fully under Cleaning Data, below. While neither registry database structures nor database requirements are standardized, the Clinical Data Interchange Standards Consortium[2] is actively working on representative models of data interchange and portability using standardized concepts and formats. Chapter 4 further discusses these models, which are applicable to registries as well as clinical trials.

2.2. Procedures, Personnel, and Data Sources

Data collection procedures need to be carefully considered in planning the operations of a registry. Successful registries depend on a sustainable workflow model that can be integrated into the day-to-day clinical practice of active physicians, nurses, pharmacists, and patients with minimal disruption. (See Chapter 10.) Programs can benefit tremendously from preliminary input from health care workers or study coordinators who are likely to be participants.

2.2.1. Pilot Testing

One method of gathering input from likely participants before the full launch of a registry is pilot testing. Whereas feasibility testing, which is discussed in Chapter 2.2.4, focuses on whether a registry should be implemented, pilot testing focuses on how it should be implemented. Piloting can range from testing a subset of the procedures, CRFs, or data capture systems, to a full launch of the registry in a limited subset of sites and patients.

The key to effective pilot testing is to conduct it at a point where the results of the pilot can still be used to modify the registry implementation. Through pilot testing, one can assess comprehension, acceptance, feasibility, and other factors that influence how readily the patient registry processes will fit into patient lifestyles and the normal practices of the health care provider. For example, some data sources may or may not be available for all patients. Chapter 4.5 discusses pilot testing in more detail.

2.2.2. Documentation of Procedures

The data collection procedures for each registry should be clearly defined and described in a detailed manual. The term *manual* here refers to the reference information in any appropriate form, including hard copy, electronic, or via interactive Web or software-based systems. Although the detail of this manual may vary from registry to registry depending on the intended purpose, the required information generally includes protocols, policies, and procedures; the data collection instrument; and a listing of all the data elements and their full definitions. If the registry has optional fields (i.e., fields that do not have to be completed on every patient), these should be clearly specified.

In addition to patient inclusion and exclusion criteria, the screening process should be specified, as should any documentation to be retained at the site level and any plans for monitoring or auditing of screening

practices. If sampling is to be performed, the method or systems used should be explained, and tools should be provided to simplify this process for the sites. The manual should clearly explain how patient identification numbers are created or assigned and how duplicate records should be prevented. Any required training for data collectors should also be described.

If paper CRFs are utilized, the manual should describe specifically how the paper CRFs are used and which parts of the forms (e.g., two-part or three-part no-carbon-required forms) should be retained, copied, submitted, or archived. If electronic CRFs are utilized, clear user manuals and instructions should be available. These procedures are an important resource for all personnel involved in the registry (and for external auditors who might be asked to assure the quality of the registry).

The importance of standardizing procedures to ensure that the registry uses uniform and systematic methods for collecting data cannot be overstated. At the same time, some level of customization of data entry methods may be required or permitted to enable the participation of particular sites or subgroups of patients within some practices. As discussed in Chapter 10, if the registry provides payments to sites for participation, then the specific requirements for site payments should be clearly documented, and this information should be provided with the registry documents.

2.2.3. Personnel

All personnel involved in data collection should be identified, and their job descriptions and respective roles in data collection and processing should be described. Examples of such "roles" include patient, physician, data entry personnel, site coordinator, help desk, data manager, and monitor. The necessary documentation or qualification required for any role should be specified in the registry documentation. As an example, some registries require personnel documentation such as a curriculum vitae, protocol signoff, attestation of intent to follow registry procedures, or confirmation of completion of specified training.

2.2.4. Data Sources

The sources of data for a registry may include new information collected from the patient, new or existing information reported by or derived from the clinician and the medical record, and ancillary stores of patient information, such as laboratories. Since registries for evaluating patient outcomes should employ uniform and systematic methods of data collection, all data-related procedures—including the permitted sources of data; the data elements and their definitions; and the validity, reliability, or other quality requirements for the data collected from each source—should be predetermined and defined for all collectors of data. As described under Quality Assurance, data quality is dependent on the entire chain of data collection and processing. Therefore, the validity and quality of the registry data as a whole ultimately derive from the least rigorous link, not the most.

In Chapter 6, data sources are classified as primary or secondary, based on the relationship of the data to the registry purpose and protocol. Primary data sources incorporate data collected for direct purposes of the registry (i.e., primarily for the registry). Secondary data sources consist of data originally collected for purposes other than the registry (e.g., standard medical care, insurance claims processing). The section below incorporates and expands on these definitions.

2.2.5. Patient-Reported Data

Patient-reported data are data specifically collected from the patient for the purposes of the registry rather than interpreted through a clinician or an indirect data source (e.g., laboratory value, pharmacy records).

Such data may range from basic demographic information to validated scales of patient-reported outcomes (PROs). From an operational perspective, a wide range of issues should be considered in obtaining data directly from patients. These range from presentation (e.g., font size, language, reading level) to technologies (e.g., paper-and-pencil questionnaires, computer inputs, telephone or voice inputs, or hand-held patient diaries). Mistakes at this level can inadvertently bias patient selection, invalidate certain outcomes, or significantly affect cost. Limiting the access for patient reporting to particular languages or technologies may limit participation. Patients with specific diagnoses may have difficulties with specific technologies (e.g., small font size for visually impaired, paper and pencil for those with rheumatoid arthritis). Other choices, such as providing a patient-reported outcomes instrument in a format or method of delivery that differs from how it was validated (e.g., questionnaire rather than interview), may invalidate the results. For more information on PRO development and use, see Chapter 5.

2.2.6. Clinician-Reported Data

Clinician-reported or -derived data can also be divided into primary and secondary. As an example, specific clinician rating scales (e.g., National Institutes of Health Stroke Scale)[3] may be required for the registry but not routinely captured in clinical encounters. Some variables might be collected directly by the clinician for the registry or obtained from the medical record. Data elements that must be collected directly by the clinician (e.g., because of a particular definition or need to assess a specific comorbidity that may or may not be routinely present in the medical record) should be specified. These designations are important because they determine who can collect the data for a particular registry or what changes must be made in the procedures that the clinician follows in recording a medical record for a patient in a registry. Furthermore, the types of error that arise in registries (discussed under Quality Assurance) will differ by the degree of use of primary and secondary sources, as well as other factors. As an example, registries that utilize medical chart abstracters, as discussed below, may be subject to more interpretive errors.[4]

2.2.7. Data Abstraction

Data abstraction is the process by which a data collector other than the clinician interacting with the patient extracts clinician-reported data. While physical examination findings, such as height and weight, or laboratory findings, such as white blood cell counts, are straightforward, abstraction usually involves varying degrees of judgment and interpretation.

Clarity of description and standardization of definitions are essential to the assurance of data quality and to the prevention of interpretive errors when using data abstraction. Knowledgeable registry personnel should be designated as resources for the data collectors in the field, and processes should be put in place to allow the data collectors in the field continuous access to these designated registry personnel for questions on specific definitions and clinical situations. Registries that span long periods, such as those intended for surveillance, might be well served by a structure that allows for the review of definitions on a periodic basis to ensure the timeliness and completeness of data elements and definitions, and to add new data elements and definitions. A new product or procedure introduced after the start of a registry is a common reason for such an update.

Abstracting data from unformatted hard copy (e.g., a hospital chart) is often an arduous and tedious process, especially if free text is involved, and it usually requires a human reader. The reader, whose qualifications may range from a trained "medical record analyst" or other health professional to an

untrained research assistant, may need to decipher illegible handwriting, translate obscure abbreviations and acronyms, and understand the clinical content to sufficiently extract the desired information. Registry personnel should develop formal chart abstraction guidelines, documentation, and coding forms for the analysts and reviewers to use.

Generally, the guidelines include instructions to search for particular types of data that will go into the registry (e.g., specific diagnoses or laboratory results). Often the analyst will be asked to code the data, using either standardized codes from a codebook (e.g., the ICD-9 [International Classification of Diseases, 9th Revision] code) corresponding to a text diagnosis in a chart, or codes that may be unique to the registry (e.g., a severity scale of 1 to 5).

All abstraction and coding instructions must be carefully documented and incorporated into a data dictionary for the registry. Because of the "noise" in unstructured, hard-copy documents (e.g., spurious marks or illegible writing) and the lack of precision in natural language, the clinical data abstracted by different abstracters from the same documents may differ. This is a potential source of error in a registry.

To reduce the potential for this source of error, registries should ensure proper training on the registry protocol and procedures, condition(s), data sources, data collection systems, and most importantly, data definitions and their interpretation. While training should be provided for all registry personnel, it is particularly important for nonclinician data abstracters. Training time depends on the nature of the source (charts or CRFs), complexity of the data, and number of data items. A variety of training methods, from live meetings to online meetings to interactive multimedia recordings, have all been used with success.[5] Training often includes test abstractions using sample charts. For some purposes, it is best practice to train abstracters using standardized test charts. Such standardized tests can be further used both to obtain data on the inter-rater reliability of the CRFs, definitions, and coding instructions and to determine whether individual abstracters can perform up to a defined minimum standard for the registry. Registries that rely on medical chart abstraction should consider reporting on the performance characteristics associated with abstraction, such as inter-rater reliability.[6] Examining and reporting on intra-rater reliability may also be useful. Some key considerations in standardizing medical chart abstractions are:

- Standardized materials (e.g., definitions, instructions).
- Standardized training.
- Testing with standardized charts.
- Reporting of inter-rater reliability.

2.2.8. Electronic Medical Record

An electronic medical record (EMR) is an electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within one health care organization. More complete than an EMR, an electronic health record (EHR) is an electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards and that can be created, managed, and consulted by authorized clinicians and staff across more than one health care organization.[7] For the purposes of this discussion, we will refer to the more limited capabilities of the EMR.

The EMR (and EHR) will play an increasingly important role as a source of clinical data for registries. The medical community is currently in a transition period in which the primary repository of a patient's

medical record is changing from the traditional hard-copy chart to the EMR. The main function of the EMR is to aggregate all clinical electronic data about a patient into one database, in the same way that a hard-copy medical chart aggregates paper records from various personnel and departments responsible for the care of the patient. Depending on the extent of implementation, the EMR may include patient demographics, diagnoses, procedures, progress notes, orders, flow sheets, medications, and allergies. The primary sources of data for the EMR are the health care providers. Data may be entered into the EMR through keyboards or touch-screens in medical offices or at the bedside. In addition, the EMR system is usually interfaced to ancillary systems (discussed below), such as laboratory, pharmacy, radiology, and pathology. Ancillary systems, which usually have their own databases, export relevant patient data to the EMR system, which imports the data into its database.

Since EMRs include the majority of clinical data available about a patient, they can be a major source of patient information for a registry. What an EMR usually does not include is registry-specific (primary source) data that are collected separately from hard-copy or electronic forms. In the next several years, suitable EMR system interfaces may be able to present data needed by registries in accordance with registry-specified requirements, either within the EMR (which then populates the registry) or in an electronic data capture system (which then populates the EMR). EMRs already serve as secondary data sources in some registries, and this practice will continue to grow as EMRs become more widely used. In these situations, data may be extracted from the EMR, transformed into registry format, and loaded into the registry, where they will reside in the registry database together with registry-specific data imported from other sources. In a sense, this is similar to medical chart abstraction except that it is performed electronically. There are two key differences. First, the data are "abstracted" once for all records. In this context, abstraction refers to the mapping and other decisionmaking needed to bring the EMR data into the registry database. It does not eliminate the potential for interpretive errors, as described later in this chapter, but it centralizes that process, making the rules clear and easily reviewed. Second, the data are uploaded electronically, eliminating duplicative data entry, potential errors associated with data reentry, and the related cost of this redundant effort.

When the EMR is used as a data source for a registry, a significant problem occurs when the information needed by the registry is stored in the EMR as free text, rather than codified or structured data. Examples of structured data include ICD-9 diagnoses and laboratory results. In contrast, physician progress notes, consultations, radiology reports, etc., are usually dictated and transcribed as narrative free text. While data abstraction of free text derived from an EMR can be done by a medical record analyst, with the increasing use of EMRs, automated methods of data abstraction from free text have been developed. *Natural language processing* (NLP) is the term given to this technology. It allows computers to process and extract information from human language. The goal of NLP is to parse free text into meaningful components based on a set of rules and a vocabulary that enable the software to recognize key words, understand grammatical constructions, and resolve word ambiguities. Those components can be extracted and delivered to the registry along with structured data extracted from the EMR, and both can be stored as structured data in the registry database.

An increasing number of NLP software packages are available (e.g., caTIES from the National Cancer Institute,[8] i2b2 – Informatics for Integrating Biology at the Bedside,[9] and a number of commercial products). However, NLP is still in an early phase of development and cannot yet be used for all-purpose chart abstraction. In general, NLP software operates in specific clinical domains (e.g., radiology,

pathology), whose vocabularies have been included in the NLP software's database. Nevertheless, NLP has been used successfully to extract diagnoses and drug names from free text in various clinical settings.

It is anticipated that EMR/EHR use will grow significantly with the incentives provided under the American Recovery and Reinvestment Act of 2009 (ARRA) health information technology provisions. Currently, only a minority of U.S. patients have their data stored in systems that are capable of retrieval at the level of a data element. Furthermore, only a small number of these systems currently store data in structured formats with standardized data definitions for those data elements that are common across different vendors. A significant amount of attention is currently focused on interchange formats between clinical and research systems (e.g., from Health Level Seven [HL-7][10] to Clinical Data Interchange Standards Consortium[11] models). Attention is also focused on problems of data syntax and semantics. The adoption of common database structures and open interoperability standards will be critical for future interchange between EHRs and registries. This topic is discussed in depth in Chapter 15.

2.2.9. Other Data Sources

Some of the clinical data used to populate registries may be derived from repositories other than EMRs. Examples of other data sources include billing systems, laboratory databases, and other registries. Chapter 6 discusses the potential uses of other data sources in more detail.

2.3. Data Entry Systems

Once the primary and any secondary data sources for a registry have been identified, the registry team can determine how data will be entered into the registry database. Many techniques and technologies exist for entering or moving data into the registry database, including paper CRFs, direct data entry, facsimile or scanning systems, interactive voice response systems (IVRS), and electronic CRFs. There are also different models for how quickly those data reach a central repository for cleaning, reviewing, monitoring, or reporting. Each approach has advantages and limitations, and each registry must balance flexibility (the number of options available) with data availability (when the central repository is populated), data validity (whether all methods are equally able to produce clean data), and cost. Appropriate decisions depend on many factors, including the number of data elements, number of sites, location (local preferences that vary by country, language differences, and availability of different technologies), registry duration, followup frequency, and available resources.

2.3.1. Paper CRFs

With paper CRFs, the clinician enters clinical data on the paper form at the time of the clinical encounters, or other data collectors abstract the data from medical records after the clinical encounter. CRFs may include a wide variety of clinical data on each patient gathered from different sources (e.g., medical chart, laboratory, pharmacy) and from multiple patient encounters. Before the data on formatted paper forms are entered into a computer, the forms should be reviewed for completeness, accuracy, and validity. Paper CRFs can be entered into the database by either direct data entry or computerized data entry via scanning systems.

With direct data entry, a computer keyboard is used to enter data into a database. Key entry has a variable error rate depending on personnel, so an assessment of error rate is usually desirable, particularly when a high volume of data entry is performed. Double data entry is a method of increasing the accuracy of manually entered data by quantifying error rates as discrepancies between two different data entry personnel; data accuracy is improved by having up to two individuals enter the data and a third person

review and manage discrepancies. With upfront data validation checks on direct data entry, the likelihood of data entry errors significantly decreases. Therefore, the choice of single vs. double data entry should be driven by the requirements of the registry for a particular maximal error rate and the ability of each method to achieve that rate in key measures in the particular circumstance. Double data entry, while a standard of practice for registrational trials, may add significant cost. Its use should be guided by the need to reduce an error rate in key measures and the likelihood of accomplishing that by double data entry as opposed to other approaches. In some situations, assessing the data entry error rates by re-entering a sample of the data is sufficient for reporting purposes.

With hard-copy structured forms, entering data using a scanner and special software to extract the data from the scanned image is possible. If data are recorded on a form as marks in checkboxes, the scanning software enables the user to map the location of each checkbox to the value of a variable represented by the text item associated with the checkbox, and to determine whether the box is marked. The presence of a mark in a box is converted by the software to its corresponding value, which can then be transmitted to a database for storage. If the form contains hand-printed or typed text or numbers, optical character recognition (OCR) software is often effective in extracting the printed data from the scanned image. However, the print font must be of high quality to avoid translation errors, and spurious marks on the page can cause errors. Error checking is based on automated parameters specified by the operator of the system for exception handling. The comments on assessing error rates in the section above are applicable for scanning systems as well.

2.3.2. Electronic CRFs (eCRFs)

An *eCRF* is defined as an auditable electronic form designed to record information required by the clinical trial protocol to be reported to the sponsor on each trial subject.[12] An eCRF allows clinician-reported data to be entered directly into the electronic system by the data collector (the clinician or other data collector). Site personnel in many registries still commonly complete an intermediate hard-copy worksheet representing the CRF and subsequently enter the data into the eCRF. While this approach increases work effort and error rates, it is not yet practical for all electronic data entry to be performed at the bedside, during the clinical encounter, or in the midst of a busy clinical day.

An eCRF may originate on local systems (including those on an individual computer, a local area network server, or a hand-held device) or directly from a central database server via an Internet-based connection or a private network. For registries that exist beyond a single site, the data from the local system must subsequently communicate with a central data system. An eCRF may be presented visually (e.g., computer screen) or aurally (e.g., telephonic data entry, such as interactive voice response systems). Specific circumstances will favor different presentations. For example, in one clozapine patient registry that is otherwise similar to Case Example 21, both pharmacists and physicians can obtain and enter data via a telephone-based interactive voice response system as well as a Web-based system. The option is successful in this scenario because telephone access is ubiquitous in pharmacies and the eCRF is very brief.

A common method of electronic data entry is to use Web-based data entry forms. Such forms may be used by patients, providers, and interviewers to enter data into a local repository. The forms reside on servers, which may be located at the site of the registry or colocated anywhere on the Internet. To access a data entry form, a user on a remote computer with an Internet connection opens a browser window and

enters the address of the Web server. Typically, a login screen is displayed and the user enters a user identification and password, provided by personnel responsible for the Web site or repository. Once the server authenticates the user, the data entry form is displayed, and the user can begin entering data. As described in Cleaning Data, many electronic systems can perform data validation checks or edits at the time of data entry. When data entry is complete, the user submits the form, which is sent over the Internet to the Web server.

Hand-held devices such as personal digital assistants (PDAs) and cell phones may also be used with Web-based or other forms to submit data to a server. Mobility has recently become an important attribute for clinical data collection. Software has been developed that enables wireless PDAs and cell phones to collect data and transmit them over the Internet to database servers in fixed locations. As wireless technology continues to evolve and data transmission rates increase, these will become more essential data entry devices for patients and clinicians.

2.4. Advantages and Disadvantages of Data Collection Technologies

When the medical record or ancillary data are in electronic format, they may be abstracted to the CRF by a data collector or, in some cases, uploaded electronically to the registry database. The ease of extracting data from electronic systems for use in a registry depends on the design of the interfaces of ancillary and registry systems, and the ability of the EMR or ancillary system software to make the requested data accessible. However, as system vendors increasingly adopt open standards for interoperability, transferring data from one system to another will likely become easier. Many organizations are actively working toward improved standards, including HL7,[10] the National eHealth Collaborative,[13] the National Institute of Standards and Technology (NIST),[14] and others. Chapter 15 describes standards and certifications specific to EHR systems.

Electronic interfaces are necessary to move data from one computer to another. If clinical data are entered into a local repository from an eCRF form or entered into an EMR, the data must be extracted from the source dataset in the local repository, transformed into the format required by the registry, and loaded into the registry database for permanent storage. This is called an "extract, transform, and load" (ETL) process. Unless the local repository is designed to be consistent with the registry database in terms of the names of variables and their values, data mapping and transformation can be a complex task. In some cases, manual transfer of the data may be more efficient and less time consuming than the effort to develop an electronic interface. Emerging open standards can enable data to be transferred from an EHR directly into the registry. This topic is discussed in more detail in Chapter 15.

If an interface between a local electronic system and registry system is developed, it is still necessary to communicate to the ancillary system the criteria for retrieval and transmission of a patient record. Typically, the ancillary data are maintained in a relational database, and the system needs to run an SQL (Structured Query Language) query against the database to retrieve the specified information. An SQL query may specify individual patients by an identifier (e.g., a medical record number) or by values or ranges of specific variables (e.g., all patients with hemoglobin A1c over 8 mg/dl). The results of the query are usually stored as a file (e.g., XML, CSV, CDISC ODM) that can be transformed and transferred to the registry system across the interface. A variety of interface protocols may be used to transfer the data.

Because data definitions and formats are not yet nationally standardized, transfer of data from an EMR or ancillary system to a registry database is prone to error. Careful evaluation of the transfer specifications

for interpretive or mapping errors is a critical step that should be verified by the registry coordinating center. Furthermore, a series of test transfers and validation procedures should be performed and documented. Finally, error checking must be part of the transfer process because new formats or other errors not in the test databases may be introduced during actual practice, and these need to be identified and isolated from the registry itself. Even though each piece of data may be accurately transferred, the data may have different representations on the different systems (e.g., value discrepancies such as the meaning of "0" vs. "1," fixed vs. floating point numbers, date format, integer length, and missing values). In summary, any system used to extract EMR records into registry databases should be validated and should include an interval sampling of transfers to ensure that uploading of this information is consistent over time.

The ancillary system must also notify the registry when an error correction occurs in a record already transferred to the registry. Registry software must be able to receive that notification, flag the erroneous value as invalid, and insert the new, corrected value into its database. Finally, it is important to recognize that the use of an electronic-to-electronic interchange requires not only testing but also validation of the integrity and quality of the data transferred. Few ancillary systems or EMR systems are currently validated to a defined standard. For registries that intend to report data to FDA or to other sponsors or data recipients with similar requirements, including electronic signatures, audit trails, and rigorous system validation, the ways in which the registry interacts with these other systems must be carefully considered.

2.5. Cleaning Data

Data cleaning refers to the correction or amelioration of data problems, including missing values, incorrect or out-of-range values, responses that are logically inconsistent with other responses in the database, and duplicate patient records. While all registries strive for "clean data," in reality, this is a relative term. How and to what level the data will be cleaned should be addressed upfront in a data management manual that identifies the data elements that are intended to be cleaned, describes the data validation rules or logical checks for out-of-range values, explains how missing values and values that are logically inconsistent will be handled, and discusses how duplicate patient records will be identified and managed.

2.5.1. Data Management Manual

Data managers should develop formal data review guidelines for the reviewers and data entry personnel to use. The guidelines should include information on how to handle missing data; invalid entries (e.g., multiple selections in a single-choice field, alphabetic data in a numeric field); erroneous entries (e.g., patients of the wrong gender answering gender-based questions); and inconsistent data (e.g., an answer to one question contradicting the answer to another one). The guidelines should also include procedures to attempt to remediate these data problems. For example, with a data error on an interview form, it may be necessary to query the interviewer or the patient, or to refer to other data sources that may be able to resolve the problem. Documentation of any data review activity and remediation efforts, including dates, times, and results of the query, should be maintained.

2.5.2. Automated Data Cleaning

Ideally, automated data checks are preprogrammed into the database for presentation at the time of data entry. These data checks are particularly useful for cleaning data at the site level while the patient or medical record is readily accessible. Even relatively simple edit checks, such as range values for

laboratories, can have a significant effect on improving the quality of data. Many systems allow for the implementation of more complex data edit checks, and these checks can substantially reduce the amount of subsequent manual data cleaning. A variation of this method is to use data cleaning rules to deactivate certain data fields so that erroneous entries cannot even be made. A combination of these approaches can also be used. For paper-based entry methods, automated data checks are not available at the time the paper CRF is being completed but can be incorporated when the data are later entered into the database.

2.5.3. Manual Data Cleaning

Data managers perform manual data checks or queries to review data for unexpected discrepancies. This is the standard approach to cleaning data that are not entered into the database at the site (e.g., for paper CRFs entered via data entry or scanning). By carefully reviewing the data using both data extracts analyzed by algorithms and hand review, data managers identify discrepancies and generate "queries" to send to the sites to resolve. Even eCRF-based data entry with data validation rules may not be fully adequate to ensure data cleaning for certain purposes. Anticipating all potential data discrepancies at the time that the data management manual and edit checks are developed is very difficult. Therefore, even with the use of automated data validation parameters, some manual cleaning is often still performed.

2.5.4. Query Reports

The registry coordinating center should generate, on a periodic basis, query reports that relate to the quality of the data received, based on the data management manual and, for some purposes, additional concurrent review by a data manager. The content of these reports will differ depending on what type of data cleaning is required for the registry purpose and how much automated data cleaning has already been performed. Query reports may include missing data, "out-of-range" data, or data that appear to be inconsistent (e.g., positive pregnancy test for a male patient). They may also identify abnormal trends in data, such as sudden increases or decreases in laboratory tests compared to patient historical averages or clinically established normal ranges. Qualified registry personnel should be responsible for reviewing the abnormal trends with designated site personnel. The most effective approach is for sites to provide one contact representative for purposes of queries or concerns by registry personnel. Depending on the availability of the records and resources at the site to review and respond to queries, resolving all queries can sometimes be a challenge. Creating systematic approaches to maximizing site responsiveness is recommended.

2.5.4. Data Tracking

For most registry purposes, tracking of data received (paper CRFs), data entered, data cleaned, and other parameters is an important component of active registry management. By comparing indicators, such as expected to observed rates of patient enrollment, CRF completion, and query rates, the registry coordinating center can identify problems and potentially take corrective action—either at individual sites or across the registry as a whole.

2.5.6. Coding Data

As further described in Chapter 4, the use of standardized coding dictionaries is an increasingly important tool in the ability to aggregate registry data with other databases. As the health information community adopts standards, registries should routinely apply them unless there are specific reasons not to use such standard codes. While such codes should be implemented in the data dictionaries during registry planning, including all codes in the interface is not always possible. Some free text may be entered as a result.

When free text data are entered into a registry, recoding these data using standardized dictionaries (e.g., MedDRA, WHODRUG, SNOMED®) may be worthwhile. There is cost associated with recoding, and in general, it should be limited to data elements that will be used in analysis or that need to be combined or reconciled with other datasets, such as when a common safety database is maintained across multiple registries and studies.

2.5.7. Storing and Securing Data

When data on a form are entered into a computer for inclusion in a registry, the form itself, as well as a log of the data entered, should be maintained for the regulatory archival period. Data errors may be discovered long after the data have been stored in the registry. The error may have been made by the patient or interviewer on the original form or during the data entry process. Examination of the original form and the data entry log should reveal the source of the error. If the error is on the form, correcting it may require reinterviewing the patient. If the error occurred during data entry, the corrected data should be entered and the registry updated. By then, the erroneous registry data may have been used to generate reports or create cohorts for population studies. Therefore, instead of simply replacing erroneous data with corrected data, the registry system should have the ability to flag data as erroneous without deleting them and to insert the corrected data for subsequent use.

Once data are entered into the registry, the registry must be backed up on a regular basis. There are two basic types of backup, and both types should be considered for use as best practice by the registry coordinating center. The first type is real-time disk backup, which is done by the disk storage hardware used by the registry server. The second is a regular (e.g., daily) backup of the registry to removable media (e.g., tape, CD-ROM, DVD). In the first case, as data are stored on disk in the registry server, they are automatically replicated to two or more physical hard drives. In the simplest example, called "mirroring," registry data are stored on a primary disk and an exact replica is stored on the mirrored disk. If either disk fails, data continue to be stored on the mirrored disk until the failed disk is replaced. This failure can be completely transparent to the user, who may continue entering and retrieving data from the registry database during the failure. More complex disk backup configurations exist, in which arrays of disks are used to provide protection from single disk failures.

The second type of periodic backup is needed for disaster recovery. Ideally, a daily backup copy of the registry database stored on removable media should be maintained off site. In case of failure of the registry server or disaster that closes the data center, the backup copy can be brought to a functioning server and the registry database restored, with the only potential loss of data being for the interval between the regularly scheduled backups. The lost data can usually be reloaded from local data repositories or re-entered from hard copy. Other advanced and widely available database solutions and disaster recovery techniques may support a "standby" database that can be located at a remote data center. In case of a failure at the primary data center, the standby database can be utilized, minimizing downtime and preventing data loss.

2.6. Managing Change

As with all other registry processes, the extent of change management will depend on the types of data being collected, the source(s) of the data, and the overall timeframe of the registry. There are two major drivers behind the need for change during the conduct of a registry: internal-driven change to refine or

improve the registry or the quality of data collected, and external-driven change that comes as a result of changes in the environment in which the registry is being conducted.

Internal-driven change is generally focused on changes to data elements or data validation parameters that arise from site feedback, queries, and query trends that may point to a question, definition, or CRF field that was poorly designed or missing. If this is the case, the registry can use the information coming back from sites or data managers to add, delete, or modify the database requirements, CRFs, definitions, or data management manual as required. At times, more substantive changes, such as the addition of new forms or changes to the registry workflow, may be desirable to examine new conditions or outcomes. External-driven change generally arises in multiyear registries as new information about the disease and/or product under study becomes available, or as new therapies or products are introduced into clinical practice. Change and turnover in registry personnel is another type of change, and one that can be highly disruptive if procedures are not standardized and documented.

A more extensive form of change may occur when a registry either significantly changes its CRFs or changes the underlying database. Longstanding registries address this issue from time to time as information regarding the condition or procedure evolves and data collection forms and definitions require updating. Chapter 14 discusses the process for making significant modifications to a registry in more detail

Proper management of change is crucial to the maintenance of the registry. A consistent approach to change management, including decisionmaking, documentation, data mapping, and validation, is an important aspect of maintaining the quality of the registry and the validity of the data. While the specific change management processes might depend on the type and nature of the registry, change management in registries that are designed to evaluate patient outcomes requires, at the very least, the following structures and processes:

- *Detailed manual of procedures*: As described earlier, a detailed manual that is updated on a regular basis—containing all the registry policies, procedures, and protocols, as well as a complete data dictionary listing all the data elements and their definitions—is vital for the functioning of a registry. The manual is also a crucial component for managing and documenting change management in a registry.
- *Governing body*: As described in Chapter 2.6, registries require oversight and advisory bodies for a number of purposes. One of the most important is to manage change on a regular basis. Keeping the registry manual and data definitions up to date is one of the primary responsibilities of this governing body. Large prospective registries, such as the National Surgical Quality Improvement Program, have found it necessary to delegate the updating of data elements and definitions to a special definitions committee.
- *Infrastructure for ongoing training*: As mentioned above, change in personnel is a common issue for registries. Specific processes and an infrastructure for training should be available at all times to account for any unanticipated changes and turnover of registry personnel or providers who regularly enter data into the registry.
- *Method to communicate change*: Since registries frequently undergo change, there should be a standard approach and timeline for communicating to sites when changes will take place.

In addition to instituting these structures, registries should also plan for change from a budget perspective (Chapter 2) and from an analysis perspective (Chapter 13).

2.7. Using Data for Care Delivery, Coordination, and Quality Improvement

2.7.1. Improving Care

As registries increasingly collect data in electronic format, the time between care delivery and data collection is being reduced. This shorter timeframe offers significant opportunities to utilize registry functionalities to improve care delivery at the patient and population levels. These functionalities (Table 14) include generating outputs that promote care delivery and coordination at the individual patient level (e.g., decision support, patient reports, reminders, notifications, lists for proactive care, educational content) and providing tools that assist with population management, quality improvement, and quality reporting (e.g., risk adjustment, population views, benchmarks, quality report transmissions). A number of registries are designed primarily for this purpose. Several large national registries[15,16,17,18] have shown large changes in performance during the course of hospital or practice participation in the registry. For example, in one head-to-head study that used hospital data from Hospital Compare, an online database created by the Centers for Medicare & Medicaid Services, patients in hospitals enrolled in the American Heart Association's Get With The Guidelines® Coronary Artery Disease (CAD) registry, which includes evidence-based reminders and real-time performance measurement reports, fared significantly better in measures of guidelines compliance than those in hospitals not enrolled in the registry.[19]

Table 14. Registry Functionalities

Inputs: Obtaining data	• Identify/enroll representative patients (e.g., sampling) • Collect data from multiple sources and settings (providers, patients, labs, pharmacies) at key points • Use uniform data elements and definitions (risk factors, treatments, and outcomes) • Check and correct data (validity, coding, etc.) • Link data from different sources at patient level (manage patient identifiers) • Maintain security and privacy (e.g., access control, audit trail)
Outputs: Care delivery and coordination	• Provide real-time feedback with decision support (evidence/guidelines) • Generate patient-level reports and reminders (longitudinal reports, care gaps, summary lists/plans, health status) • Send relevant notifications to providers and patients (care gaps, prevention support, self-management) • Share information with patients and other providers • List patients/subgroups for proactive care • Link to relevant patient education
Outputs: Population measurement and quality improvement	• Provide population-level reports o Real-time/rapid cycle o Risk adjusted o Including standardized measures o Including benchmarks o Enabling different reports for different levels of users • Enable ad hoc reports for exploration • Provide tools to manage populations or subgroups • Generate dashboards that facilitate action • Facilitate third-party quality reporting (transmission)

2.7.2. Special Case: Performance-Linked Access System

A performance-linked access system (PLAS), also known as a restricted access or limited distribution system, is another application of a registry to serve more than an observational goal. Unlike a disease and exposure registry, a PLAS is part of a detailed risk-minimization action plan that sponsors develop as a commitment to enhance the risk-benefit balance of a product when approved for the market. The purpose of a PLAS is to mitigate a certain known drug-associated risk by ensuring that product access is linked to a specific performance measure. Examples include systems that monitor laboratory values, such as white blood cell counts during clozapine administration to prevent severe leukopenia, or routine pregnancy testing during thalidomide administration to prevent in utero exposure to this known teratogenic compound. Additional information on PLAS can be found in *Guidance for Industry: Development and Use of Risk Minimization Action Plans*.[20]

3. Quality Assurance

In determining the utility of a registry for decisionmaking, it is critical to understand the quality of the procedures used to obtain the data and the quality of the data stored in the database. As patient registries that meet sufficient quality criteria (discussed in Chapters 1 and 25) are increasingly being seen as important means to generate evidence regarding effectiveness, safety, and quality of care, the quality of data within the registry must be understood in order to evaluate its suitability for use in decisionmaking. Registry planners should consider how to assure quality to a level sufficient for the intended purposes (as described below) and should also consider how to develop appropriate quality assurance plans for their registries. Those conducting the registry should assess and report on those quality assurance activities.

Methods of quality assurance will vary depending on the intended purpose of the registry. A registry intended to serve as key evidence for decisionmaking[21] (e.g., coverage determinations, product safety evaluations, or performance-based payment) will require higher levels of quality assurance than a registry describing the natural history of a disease. Quality assurance activities generally fall under three main categories: (1) quality assurance of data, (2) quality assurance of registry procedures, and (3) quality assurance of computerized systems. Since many registries are large, the level of quality assurance that can be obtained may be limited by budgetary constraints.

To balance the need for sufficient quality assurance with reasonable resource expenditure for a particular purpose, a risk-based approach to quality assurance is highly recommended. A risk-based approach focuses on the most important sources of error or procedural lapses from the perspective of the registry's purpose. Such sources of error should be defined during inception and design phases. As described below, registries with different purposes may be at risk for different sources of error and focus on different practices and levels of assessment. Standardization of methods for particular purposes (e.g. national performance measurement) will likely become more common in the future if results are to be combined or compared between registries.

3.1. Assurance of Data Quality

Structures, processes, policies, and procedures need to be put in place to ascertain the quality of the data in the registry and to ensure against several types of errors, including:

- *Errors in interpretation or coding*: An example of this type of error would be two abstracters looking for the same data element in a patient's medical record but extracting different data from the same chart. Variations in coding of specific conditions or procedures also fall under the

category of interpretive errors. Avoidance or detection of interpretive error includes adequate training on definitions, testing against standard charts, testing and reporting on inter-rater reliability, and re-abstraction.

- *Errors in data entry, transfer, or transformation accuracy*: These occur when data are entered into the registry inaccurately—for example, a laboratory value of 2.0 is entered as 20. Avoidance or detection of accuracy errors can be achieved through upfront data quality checks (such as ranges and data validation checks), reentering samples of data to assess for accuracy (with the percent of data to be sampled depending on the study purpose), and rigorous attention to data cleaning.
- *Errors of intention*: Examples of intentional distortion of data (often referred to as "gaming") are inflated reporting of preoperative patient risk in registries that compare risk-adjusted outcomes of surgery, or selecting only cases with good outcomes to report ("cherry-picking"). Avoidance or detection of intentional error can be challenging. Some approaches include checking for consistency of data between sites, assessing screening log information against other sources (e.g., billing data), and performing onsite audits (including monitoring source records) either at random or "for cause."

Steps for assuring data quality include:

- *Training*: Educate data collectors/abstracters in a structured manner.
- *Data completeness*: When possible, provide sites with immediate feedback on issues such as missing or out-of-range values and logical inconsistencies.
- *Data consistency*: Compare across sites and over time.
- *Onsite audits for a sample of sites*: Review screening logs and procedures and/or samples of data.
- *For-cause audits*: Use both predetermined and data-informed methods to identify potential sites at higher suspicion for inaccuracy or intentional errors, such as discrepancies between enrollment and screening logs, narrow data ranges, and overly high or low enrollment.

To further minimize or identify these errors and to ensure the overall quality of the data, the following should be considered.

3.1.1. A Designated Individual Accountable for Data Quality at Each Site

Sites submitting data to a registry should have at least one person who is accountable for the quality of these data, irrespective of whether the person is collecting the data as well. The site coordinator should be fully knowledgeable of all protocols, policies, procedures, and definitions in a registry. The site coordinator should ensure that all site personnel involved in the registry are knowledgeable and that all data transmitted to registry coordinating centers are valid and accurate.

3.1.2. Assessment of Training and Maintenance of Competency of Personnel

Thorough training and documentation of maintenance of competency, for both site and registry personnel, are imperative to the quality of the registry. A detailed and comprehensive operations manual, as described earlier, is crucial for the proper training of all personnel involved in the registry. Routine cognitive testing (surveys) of health care provider knowledge of patient registry requirements and appropriate product use should be performed to monitor maintenance of the knowledge base and compliance with patient registry requirements. Retraining programs should be initiated when survey results provide evidence of lack of knowledge maintenance. All registry training programs should provide means by which the knowledge of the data collectors about their registries and their competence in data

collection can be assessed on a regular basis, particularly when changes in procedures or definitions are implemented.

3.1.3. Data Quality Audits

As described above, the level to which registry data will be cleaned is influenced by the objectives of the registry, the type of data being collected (e.g., clinical data vs. economic data), the sources of the data (e.g., primary vs. secondary), and the timeframe of the registry (e.g., 3-month followup vs. 10-year followup). These registry characteristics often affect the types and number of data queries that are generated, both electronically and manually. In addition to identifying missing values, incorrect or out-of-range values, or responses that are logically inconsistent with other responses in the database, specifically trained registry personnel can review the data queries to identify possible error trends and to determine whether additional site training is required. For example, such personnel may identify a specific patient outcome question or eCRF field that is generating a larger than average proportion of queries, either from one site or across all registry sites. Using this information, the registry personnel can conduct targeted followup with the sites to retrain them on the correct interpretation of the outcome question or eCRF field, with the goal of reducing the future query rate on that particular question or field. These types of "training tips" can also be addressed in a registry newsletter as a way to maintain frequent but unobtrusive communication with the registry sites.

If the registry purpose requires more stringent verification of the data being entered into the database by registry participants, registry planners may decide to conduct audits of the registry sites. Like queries discussed above, the audit plan for a specific registry will be influenced by the purpose of the registry, the type of data being collected, the source of the data, and the overall timeframe of the registry. In addition, registry developers must find the appropriate balance between the extensiveness of an audit and the impact on overall registry costs. Based on the objectives of the registry, a registry developer can define specific data fields (e.g., key effectiveness variables or adverse event data) on which the audit can be focused.

The term *audit* may describe examination or verification, may take place onsite (sometimes called monitoring) or offsite, and may be extensive or very limited. The audit can be conducted on a random sample of participating sites (e.g., 5–20 percent of registry sites); "for cause" (meaning only when there is an indication of a problem, such as one site being an outlier compared with most others); on a random sample of patients; or using sampling techniques based on geography, practice setting (academic center vs. community hospital), patient enrollment rate, or query rate ("risk-based" audit strategy).

The approach to auditing the quality of the data should reflect the most significant sources of error with respect to the purpose of the registry. For example, registries used for performance measurement may have a higher risk of exclusion of higher risk patients ("cherry-picking"), and the focus of an audit might be on external sources of data to verify screening log information (e.g., billing data) in addition to data accuracy. (See Case Example 22.) Finally, the timeframe of the registry may help determine the audit plan. A registry with a short followup period (e.g., 3 months) may require only one round of audits at the end of the study, prior to database lock and data analysis. For example, in the OPTIMIZE-HF registry, a data quality audit was performed, based on predetermined criteria, on a 5-percent random sample of the first 10,000 patient records verified against source documents.[22] For registries with multiyear followup, registry personnel may conduct site audits every 1 or 2 years for the duration of the registry.

In addition to the site characteristics mentioned above, sites that have undergone significant staffing changes during a multiyear registry should be considered prime audit targets to help confirm adequate training of new personnel and to quickly address possible inter-rater variability. To minimize any impact on the observational nature of the registry, the audit plan should be documented in the registry manual.

Registries that are designed for the evaluation of patient outcomes and the generation of scientific information, and that utilize medical chart abstracters, should assess inter-rater reliability in data collection with sufficient scientific rigor for their intended purpose(s). For example, in one registry that uses abstractions extensively, a detailed system of assessing inter-rater reliability has been devised and published; in addition to requiring that abstracters achieve a certain level of proficiency, a proportion of charts are scheduled for re-abstraction on the basis of predefined criteria. Statistical measures of reliability from such re-abstractions are maintained and reported (e.g., kappa statistic).[23]

Subsequent to audits (onsite or remote), communication of findings with site personnel should be conducted face to face, along with followup written communication of findings and opportunities for improvement. As appropriate to meet registry objectives, the sponsor may request corrective actions from the site. Site compliance may also be enhanced with routine communication of data generated from the patient registry system to the site for reconciliation.

3.2. Registry Procedures and Systems

3.2.1. External Audits of Registry Procedures

If registry developers determine that external audits are necessary to assure the level of quality for the specific purpose(s) of the registry, they should be conducted in accordance with preestablished criteria. Preestablished criteria could include monitoring of sites with high patient enrollment or prior audit history with findings that require attention, or monitoring could be based on level of site experience, rate of serious adverse event reporting, or identified problems. The registry coordinating center may perform monitoring of a sample of sites, which could be focused on one or several areas. This approach could range from reviewing procedures and interviewing site personnel, to checking screening logs, to monitoring individual case records.

The importance of having a complete and detailed registry manual that describes policies, structures, and procedures cannot be overemphasized in the context of quality assurance of registry procedures. Such a manual serves both as a basis for conducting the audits and as a means of documenting changes emanating from these audits. As with data quality audits, feedback of the findings of registry procedure audits should be communicated to all stakeholders and documented in the registry manual.

3.2.2. Assurance of System Integrity and Security

All aspects of data management processes should fall under a rigorous life-cycle approach to system development and quality management. Each process is clearly defined and documented. The concepts described below are consistent across many software industry standards and health care industry standards (e.g., 21 CFR Part 11, legal security standards), although some specifics may vary. The processes and procedures described should be regularly audited by an internal quality assurance function at the registry coordinating center. When third parties other than the registry coordinating center perform activities that interact with the registry systems and data, they are typically assessed for risk and are subject to regular audits by the registry coordinating center.

3.2.3. System Development and Validation

All software systems used for patient registries should follow the standard principles of software development, including following one of the standard software development life cycle (SDLC) models that are well described in the software industry.

In parallel, quality assurance of system development utilizes approved specifications to create a validation plan for each project. Test cases are created by trained personnel and systematically executed, with results recorded and reviewed. Depending on regulatory requirements, a final validation report is often written and approved. Unresolved product and process issues are maintained and tracked in an issue tracking or CAPA (Corrective Action/Preventive Action) system.

Processes for development and validation should be similarly documented and periodically audited. The information from these audits is captured, summarized, and reviewed with the applicable group, with the aim of ongoing process improvement and quality improvement.

3.3. Security

All registries maintain health information, and therefore security is an important issue. This section discusses security regulations that are applicable to U.S. registries; registries collecting data in other countries may need to comply with additional or different regulations. The HIPAA (Health Insurance Portability and Accountability Act of 1996) Security Rule lists the standards for security for electronic protected health information to be implemented by health plans, health care clearinghouses, and certain health care providers.[24] Although these standards are specific to electronic protected health information, the principles themselves are more broadly applicable. Security is achieved not simply by technology but by clear processes and procedures. Overall responsibility for security is typically assigned. Security procedures are well documented and posted. The documentation is also used to train staff. Some registries may also maintain personal information, such as information needed to contact patients to remind them to gather or submit patient-reported outcome information. The Federal Government, as well as most U.S. States and territories, have enacted legislation regarding the safekeeping of personal information and requirements for reporting notification of certain security breaches involving personal information. Specific requirements vary by State.

3.3.1. System Security Plan

A system security plan consists of documented policies and standard operating procedures defining the rules of systems, including administrative procedures, physical safeguards, technical security services, technical security mechanisms, electronic signatures, and audit trails, as applicable. The rules delineate roles and responsibilities. Included in the rules are the policies specifying individual accountability for actions, access rights based on the principle of least privilege, and the need for separation of duties. These principles and the accompanying security practices provide the foundation for the confidentiality and integrity of registry data. The rules also detail the consequences associated with noncompliance.

3.3.2. Security Assessment

Clinical data maintained in a registry can be assessed for the appropriate level of security. Standard criteria exist for such assessments and are based on the type of data being collected. Part of the validation process is a security assessment of the systems and operating procedures. One of the goals of such an assessment is effective risk management, based on determining possible threats to the system or data and identifying potential vulnerabilities.

3.3.3. Education and Training

All staff members of the registry coordinating center should be provided with periodic training on aspects of the overall systems, security requirements, and any special requirements of specific patient registries. Individuals should receive training relating to their specific job responsibilities and document that appropriate training has been received.

3.3.4. Access Rights

Access to systems and data should be based on the principles of least privilege and separation of duties. No individual should be assigned access privileges that exceed job requirements, and no individual should be in a role that includes access rights that would allow circumvention of controls or the repudiation of actions within the system. In all cases, access should be limited to authorized individuals.

3.3.5. Access Controls

Access controls provide the basis for authentication and logical access to critical systems and data. Since the authenticity, integrity, and auditability of data stored in electronic systems depend on accurate individual authentication, management of electronic signatures (discussed below) is an important topic.

Logical access to systems and computerized data should be controlled in a way that permits only authorized individuals to gain access to the system. This is normally done through a unique access code, such as a unique user ID and password combination that is assigned to the individual whose identity has been verified and whose job responsibilities require such access. The system should require the user to change the password periodically and should detect possible unauthorized access attempts, such as multiple failed logins, and automatically deauthorize the user account if they occur. The identification code can also be an encrypted digital certificate stored on a password-protected device or a biometric identifier that is designed so that it can be used only by the designated individual.

Rules should be established for situations in which access credentials are compromised. New password information should be sent to the individual by a secure method.

Intrusion detection and firewalls should be employed on sites accessible to the Internet, with appropriate controls and rules in place to limit access to authorized users. Desktop systems should be equipped with antivirus software, and servers should run the most recent security patches. System security should be reviewed throughout the course of the registry to ensure that management, operational, personnel, and technical controls are functioning properly.

3.3.6. Data Enclaves

With the growth of clinical data and demands for increasing amounts of clinical data by multiple parties and researchers, new approaches to access are evolving. Data enclaves are secure, remote-access systems that allow researchers to share respondents' information in a controlled and confidential manner.[25] The data enclave utilizes statistical, technical, and operational controls at different levels chosen for the specific viewer. This can be useful both for enhancing protection of the data and for enabling certain organizations to access data in compliance with their own organization or agency requirements. Data enclaves also can be used to allow other researchers to access a registry's data in a controlled manner. With the growth of registries and their utility for a number of stakeholders, data enclaves will become increasingly important.

3.3.7. Electronic Signatures

Electronic signatures provide one of the foundations of individual accountability, helping to ensure an accurate change history when used in conjunction with secure, computer-generated, time-stamped audit trails. Most systems utilize an electronic signature. For registries that report data to FDA, such signatures must meet criteria specified in 21 CFR Part 11 for general signature composition, use, and control (11.100, 11.200, and 11.300). However, even registries that do not have such requirements should view these as reasonable standards. Before an individual is assigned an electronic signature, it is important to verify the person's identity and train the individual in the significance of the electronic signature. In cases where a signature consists of a user ID and a password, both management and technical means should be used to ensure uniqueness and compliance with password construction rules. Password length, character composition, uniqueness, and validity life cycle should be based on industry best practices and guidelines published by the NIST. Passwords that are used in electronic signatures should abide by the same security and aging constraints as those listed for system access controls.

3.3.8. Validation

Systems that store electronic records (or depend on electronic or handwritten signatures of those records) that are required to be acceptable to FDA must be validated according to the requirements set forth in the 21 CFR Part 11 Final Rule,[26] dated March 20, 1997. The rule describes the requirements and controls for electronic systems that are used to fulfill records requirements set forth in agency regulations (often called "predicate rules") and for any electronic records submitted to the agency. FDA publishes nonbinding guidance documents from time to time that outline its current thinking regarding the scope and application of the regulation. The current guidance document is *Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application*,[27] dated August 2003. Other documents that are useful for determining validation requirements of electronic systems are *Guidance for Industry, Computerized Systems Used in Clinical Investigations*,[28] dated May 2007, and *General Principles of Software Validation; Final Guidance for Industry and FDA Staff*,[29] dated January 11, 2002.

4. Resource Considerations

Costs for registries can be highly variable, depending on the overall goals. Costs are also associated with the total number of sites, the total number of patients, and the geographical reach of the registry program. Each of the elements described in this chapter has an associated cost. Table 15 provides a list of some of the activities of the registry coordinating center as an example. Not all registries will require or can afford all of the functions, options, or quality assurance techniques described in this chapter. Registry planners must evaluate benefit vs. available resources to determine the most appropriate approach to achieve their goals.

Table 15. Data Activities Performed During Registry Coordination

Data Management	• Defines all in-process data quality control steps, procedures, and metrics. • Defines the types of edit checks that are run against the data. • Defines required file-format specifications for electronic files, as well as schedules and processes for transfers of data. • Defines quality acceptance criteria for electronic data, as well as procedures for handling exceptions. • Develops guidelines for data entry. • Identifies areas of manual review where electronic checks are not effective.

	• Develops and maintains process for reviewing, coding, and reporting adverse event data. • Develops and maintains archiving process. • Develops and documents the process for change management. • Develops and maintains process for query tracking and creates standard reports to efficiently identify outstanding queries, query types per site, etc. • Relates queries to processes and activities (e.g., CRF design) requiring process improvements. • Follows up on query responses and errors identified in data cleaning by performing accurate database updates. • Defines registry-specific dictionaries and code lists. • Performs database audits as applicable. • Conducts user testing of systems and applications per written specifications. • Establishes quality criteria and quality error rate acceptance limits. • Evaluates data points that should be audited and identifies potential sources of data errors for audits. • Identifies root cause of errors in order to recommend change in process/technology to assure the error does not occur again (continuous improvement). • Ensures that sampling audit techniques are valid and support decisions made about data. • Outlines all other data flow, including external data sources.
Documentation	• Documents the process, procedures, standards, and checklist(s) and provides training. • Documents and maintains process and standards for identifying signals and trends in data. • Documents database quality control actions performed.
Reporting	• Generates standard reports of missing data from the patient database. • Creates tools to track and inventory CRFs, and reports anticipated vs. actual CRF receipts.

Note: CRF = case report form.

References for Chapter 11

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Case Examples for Chapter 11

Case Example 21. Developing a Performance-Linked Access System

Description	The Teva Clozapine Patient Registry is one of several national patient registries for patients taking clozapine. The registry is designed as a performance-linked access system (PLAS) mandated by the U.S. Food and Drug Administration (FDA) to comply with a Risk Evaluation Mitigation Strategy (REMS). The goal is to prevent clozapine rechallenge in patients at risk for developing clozapine- induced agranulocytosis by monitoring lab data for signs of leukopenia or granulocytopenia.
Sponsor	Teva Pharmaceuticals USA
Year Started	1997
Year Ended	Ongoing
No. of Sites	Over 50,000 active physicians and pharmacies
No. of Patients	57,000 active patients

Challenge

Clozapine is classified as an atypical antipsychotic and is indicated for patients with severe schizophrenia who fail standard therapy, and for reducing the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder. However, clozapine is known to be associated with a risk of developing agranulocytosis, a potentially life threatening condition. The primary goal of the registry is to prevent clozapine-induced agranulocytosis. Patients at risk of developing clozapine-induced agranulocytosis are those who have a history of severe leukopenia or granulocytopenia (WBC <2,000/mm^3 or ANC <1,000/mm^3).

Because of the potential serious side effects, FDA requires manufacturers of clozapine to maintain a patient monitoring system. Designed as a performance-linked access system, the registry needs to assure the eligibility of patients, pharmacies, and physicians; monitor white blood cell (WBC) and absolute neutrophil (ANC) reports for low counts; assure compliance with lab report submission timelines; and respond to inquiries and reports of adverse events.

Proposed Solution

The risk of developing agranulocytosis is mitigated by regular hematological monitoring and is a condition of access to the drug, also known as the “no-blood/no drug” requirement. Since there are multiple manufacturers of clozapine, FDA requires each company to share information with the single national non-rechallenge master file (NNRMF). The registry was developed to meet these goals. The core components of the system are a call center, a website and a reminder system. Patients must be enrolled prior to receiving clozapine, and they must be assigned to a dispensing pharmacy and treating physician. After the patient has initiated therapy, a current and acceptable WBC count and ANC value are required prior to dispensing clozapine. Once a patient is enrolled and eligibility is confirmed, a 1-, 2-,

or 4-week supply of clozapine can be dispensed, depending on patient experience and the physician's prescription.

Health care professionals are required to submit laboratory reports to the registry based on the patients' monitoring frequency. Patients are monitored weekly for the first 6 months. If there are no low counts, the patient can be monitored every 2 weeks for an additional 6 months. Afterward, if no low counts are detected after continuous therapy, the patient may qualify for monitoring every 4 weeks (depending on the physician's prescription). The registry provides reminders if laboratory data are not submitted according to the schedule. If a low count is identified, registry staff inform the health care providers to make sure that they are aware of the event and appropriate action is taken. If severe leukopenia or granulocytopenia is detected, the patient is posted to the NNRMF to prevent future exposure to the drug.

Results

Results indicate that the registry is achieving its goal of reducing the risk of agranulocytosis associated with the use of clozapine by serving as an early warning system. By linking access to clozapine to a strict schedule of laboratory data submissions, the sponsor can ensure that only eligible patients are taking the drug. The sponsor is also able to detect low counts, prevent inappropriate rechallenge (or re-exposure) in at-risk patients, and monitor the patient population for any adverse events. This system provides the sponsor with data on the frequency and severity of adverse events while ensuring that only the proper patient population receives the drug.

Key Point

A PLAS can ensure that only appropriate patients receive treatment. A secure, fully functional website allows health care professionals to manage their patients electronically. A reminder system permits rapid notification to providers to assure appropriate actions are taken when low counts are detected or if lab reports are not submitted in a timely manner. A call center with after-hours service assures 24/7 availability, and data sharing with the NNRMF prevents rechallenge regardless of manufacturer. These systems can also help sponsors monitor the patient population to learn more about adherence, compliance and the frequency of adverse events.

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Case Example 22. Using Audits to Monitor Data Quality

Description	The Vascular Study Group of New England (VSGNE) is a voluntary, cooperative group of clinicians, hospital administrators, and research personnel, organized to improve the care of patients with vascular disease. The purpose of the registry is to collect and exchange information to support continuous improvements in the quality, safety, effectiveness, and cost of caring for patients with vascular disease.
Sponsor	Funded by participating institutions. Initial funding was provided by the Centers for Medicare & Medicaid Services (CMS).
Year Started	2002
Year Ended	Ongoing
No. of Sites	30 hospitals in Connecticut, Rhode Island, Massachusetts, Maine, New Hampshire, and Vermont
No. of Patients	Over 25,000

Challenge

VSGNE established a registry in 2002 as part of an effort to improve quality of care for patients undergoing carotid endarterectomy, carotid stenting, lower extremity arterial bypass, and open and endovascular repair of abdominal aortic aneurysms. The registry collects more than 120 patient, process, and outcome variables for each procedure at the time of hospitalization, and 1-year results are collected during a followup visit at the treating physician's office. All patients receiving one of the procedures of interest at a participating hospital are eligible for enrollment in the registry.

In considering the areas of greatest risk in evaluating the quality of this registry, the registry developers determined that incomplete enrollment of eligible patients was one major potential area for bias. It was determined that an audit of included vs. eligible patients could reasonably address whether this was a significant issue. However, the group needed to overcome two logistical challenges: (1) the audit had to review thousands of eligible patients at participating hospitals in a timely, cost-effective manner; and (2) the audit could not overburden the hospitals, as they participate in the study voluntarily.

Proposed Solution

The registry team developed a plan to conduct the audit using electronic claims data files from the hospitals. Each hospital was asked to send claims data files for the appropriate time periods and procedures of interest to the registry. The registry team at Dartmouth-Hitchcock Medical Center then matched the claims data to the registry enrollment using ICD-9 (International Classification of Diseases, 9th Revision) codes with manual review of some patient files that did not match using a computer-matching process.

Results

The first audit performed in 2003 found that approximately 7 percent of eligible patients had not been enrolled in the registry. Because of concerns that the missing patients may have had different outcomes than the patients who had been enrolled in the registry, the registry team asked participating hospitals

to complete registry forms for all missing patients. This effort increased the percentage of eligible patients enrolled in the registry to over 99 percent. The team also compared the discharge status of the missing patients and the enrolled patients, and found no significant differences in outcomes. The team concluded that the patients had been missed at random and that there were no systematic enrollment issues. Discussions with the hospitals identified the reasons for not enrolling patients as confusion about eligibility requirements, training issues, and questions about informed consent requirements.

Subsequent audits in 2006 and 2008 had similar outcomes, but considerable time was required to clarify ICD-9 coding differences with procedures in the registry, since ICD-9 codes are not granular for vascular procedures. In 2011, the VSGNE model for regional vascular quality improvement was adopted by the Society for Vascular Surgery (SVS) as the Vascular Quality Initiative, now a national network of regional quality groups like VSGNE, organized under the umbrella of the SVS Patient Safety Organization. In 2012, the now nationwide audit mechanism for data completeness switched from using ICD-9 codes to physician CPT claims data, since CPT codes are more precise for specific vascular procedures. Preliminary results in 2012 show more precise matching with registry data using CPT-based claims.

Key Point

For many registries, audits are an important tool for ensuring that the data are reliable and valid. However, registries that rely on voluntary site participation must be cautious to avoid overburdening sites during the audit process. A remote audit using readily available electronic files, such as claims files, provided a reasonable assessment of the percentage of eligible patients enrolled in the registry without requiring large amounts of time or resources from participating sites.

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Chapter 12. Adverse Event Detection, Processing, and Reporting

1. Introduction

Registries that collect information on specific drugs and medical devices need to anticipate the need for adverse event (AE) detection, processing, and reporting. This chapter addresses the identification, processing, and reporting of AEs detected in situations in which a registry has contact with individual patients. This document is not a formal regulatory or legal document; therefore, any information or suggestions presented herein do not supersede, replace, or otherwise interpret Federal guidance documents that touch on these subjects. Registry sponsors are encouraged to discuss plans for AE collection and processing with local health authorities when planning a registry.

This chapter is primarily focused on AEs related to pharmaceutical products. Medical devices are significantly different from pharmaceuticals in the manner in which AEs and product problems (complaints) present themselves, in the etiology of their occurrence, and in the regulation governing the defining and reporting of these occurrences, as well as postapproval study requirements. Other sources provide more information about defining and reporting of device-related AEs and product problems, and about postmarketing studies (including those involving registries).[1 2 3]

2. Identifying and Reporting Adverse Drug Events

The U.S. Food and Drug Administration (FDA) defines an adverse drug experience as any AE associated with the use of a drug in humans, whether or not considered drug related,[4] while the International Conference on Harmonisation guideline ICH E2A similarly defines an AE as an untoward medical occurrence in a patient administered a pharmaceutical product, whether or not the occurrence is related to or considered to have a causal relationship with the treatment.[5]

For marketed products regulated by FDA, AEs are categorized for reporting purposes according to the seriousness and expectedness of the event (i.e., previously observed and included in local product labeling), as it is presumed that all spontaneously reported events are potentially related to the product for the purposes of FDA reporting. Prior to marketing approval, relatedness is an additional determinant for reporting events occurring during clinical trials or preclinical studies associated with investigational new drugs and biologics. For AEs occurring in postapproval studies and reported during planned contacts and active solicitation of information from patients, as when registries collect data regarding one or more FDA-approved products,[6 7] the requirements for mandatory reporting also include whether or not there is a reasonable possibility that the drug caused the adverse experience.4 For registries that do not actively solicit AEs, incidentally reported events (e.g., those reported during clinician or consumer contact for another purpose) should typically be handled and evaluated as spontaneously reported events.

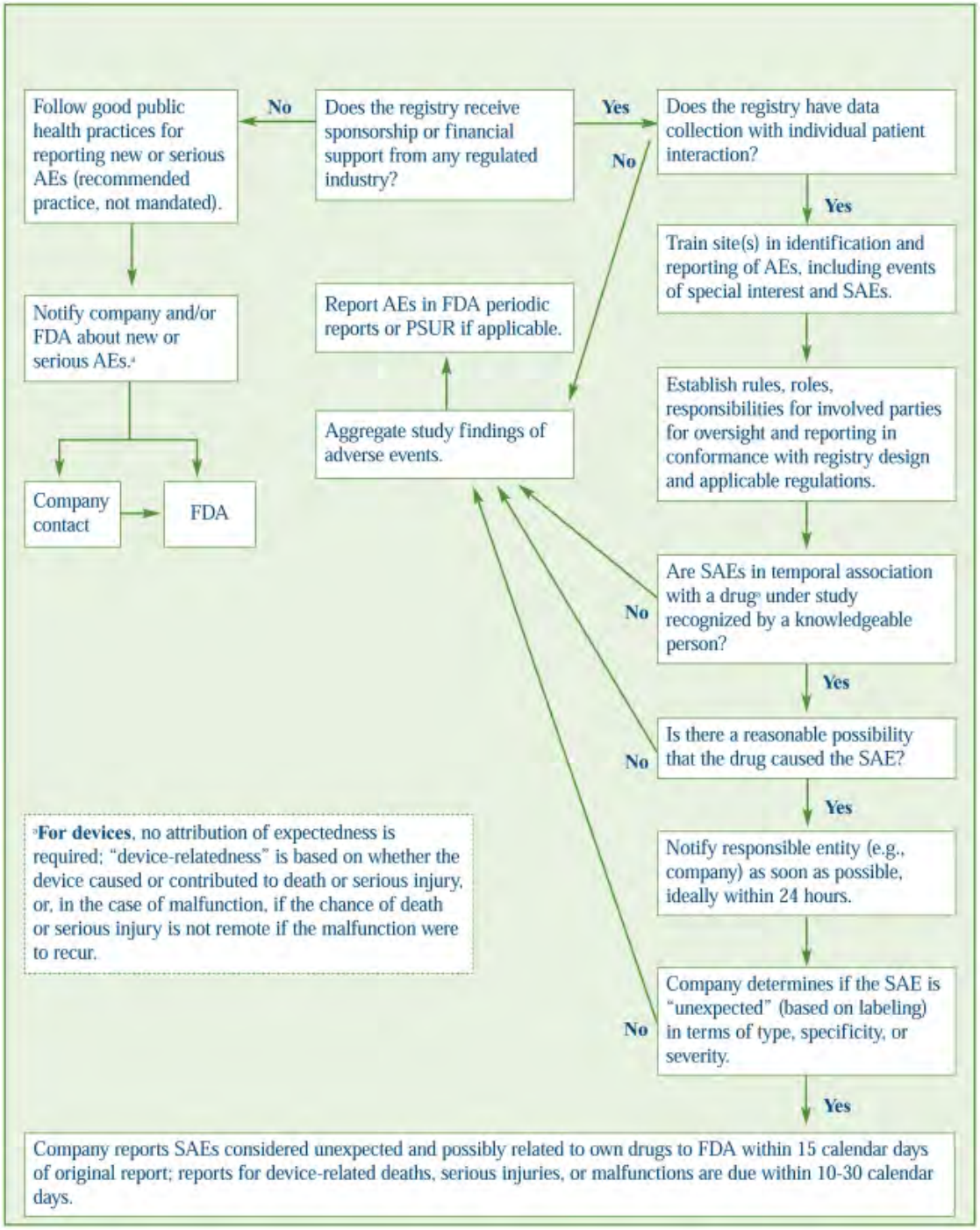
The medical device reporting (MDR) regulations differ from those for drugs and biologics in that reportable events include both AEs and problems with the device itself.[8] MDR reporting is required for incidents in which the device may have caused or contributed to a death or serious injury, or may have malfunctioned and would likely cause or contribute to death or serious injury if the malfunction were to recur.[9]

Most registries have the opportunity to identify and capture information on AEs for biopharmaceutical products and/or medical devices. With the passing of the FDA Amendments Act (FDAAA) in September 2007 and the increased emphasis on ongoing monitoring of safety profiles, evaluation of risks unknown at the time of product approval, and proactive detection of potential safety issues, registries increasingly continue to be used to fulfill safety-related objectives.[10] Although there are no regulations in the United States that specifically compel registries to capture and process AE reports (aside from reporting requirements for registries that are sponsored by regulated industries), there is an implicit requirement from the perspective of systematic data collection and promoting public health: any individual who believes a serious risk may be associated with exposure to a medical product should be encouraged to report this AE either to the product sponsor or directly to FDA. The FDA maintains MedWatch, a web-based reporting system that allows consumers and health professionals to voluntarily report serious adverse events and other serious problems that they suspect are associated with the use of an FDA-regulated product.[11]

The minimum dataset required to consider information as a reportable AE is indeed minimal, namely (1) an identifiable patient, (2) an identifiable reporter, (3) product exposure, and (4) an event. However, in addition to direct data collection, AEs can be detected through retrospective analysis of a population database, where direct patient or health care provider contact does not occur. Patient interactions include clinical interactions and data collection by phone, Internet, or other means; perusal of electronic medical records or insurance claims data would not be considered direct patient interaction. Reporting is rarely required for individual AEs observed in aggregate population data, since there is no direct patient interaction where an association might be suggested or inferred. Nevertheless, if aggregate or epidemiologic analyses suggest that an AE is associated with exposure to a drug or medical product, it is desirable that the minimum dataset information be forwarded to the manufacturer of the product, who will determine any need for, and timing of, reporting of study results to the relevant regulatory authorities.

Figure 4 provides a broad overview of the reporting requirements for AEs and shows how the reporting differs according to whether the registry has direct patient interaction, and whether it receives sponsorship and/or financial support from a regulated industry.[12] These industries may include entities with products subject to FDA regulation, including products with FDA approval, an FDA-granted license, and investigational products; and other entities such as manufacturers, user facilities, and distributors.

Figure 4. Best Practices for Adverse Event Reporting to FDA by Registries of Postmarket Products



Note: AE = adverse event; SAE = serious adverse event; FDA = U.S. Food and Drug Administration; PSUR = periodic safety update report.

All AE reporting begins with a suspicion by the physician (or responsible person who obtains or receives information) that a patient exposed to a medicinal product has experienced some AE and that the event has a reasonable possibility of being causally related to the product being used; this is referred to as the "becoming aware" principle. Some registries also collect and record AEs reported directly by the patients

or their caregivers. It is important to develop a plan for detecting, processing, and reporting AEs for any registry that has direct patient contact. If the registry receives sponsorship in whole or part from a regulated industry (for drugs or devices), the sponsor has mandated reporting requirements, including stringent timelines. AE reporting requirements for registry sponsors are discussed later in this chapter.

Prior to registry launch, the process for detecting and reporting AEs should be established in collaboration with the sponsor and any oversight committees. (See Chapter 2.) Once the plans have been developed, the registry operator or sponsor should provide training to the physicians or other responsible parties (referred to as "sites" hereafter) on how to identify AEs and to whom they should be reported. AE reporting is based on categorization of the AE according to the seriousness of the event, its expectedness based on product labeling, and presumed causality or possible association with use of the product, as follows:

- *Seriousness:* Serious AEs (SAEs) include events that result in death, are life threatening (an event in which the patient was at risk of death at the time of the event), require or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in a congenital anomaly. Important medical events may also be considered serious when, based on medical judgment, they may jeopardize the person exposed and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., death or prolonged hospitalization).
- *Expectedness:* All AEs that are previously unobserved or undocumented are referred to as "unexpected," in that their nature and severity are not consistent with information provided in the relevant product information (e.g., approved professional package insert or product label). Determination of expectedness is made by the sponsor on a case-by-case basis. Expected events typically do not require expedited reporting to the regulatory authorities.
- *Relatedness:* Relatedness is a term intended to indicate that a determination has been made that the event had a reasonable possibility of being related to exposure to the product. This assessment of causality may be based on factors such as biological plausibility, prior experience with the product, and temporal relationship between product exposure and onset of the event, as well as dechallenge (discontinuation of the product to determine if the AE resolves) and rechallenge (reintroduction of the product to determine if the AE recurs). Many terms and scales are used to describe the degree of causality, including terms such as *certainly, definitely, probably, possibly*, or *likely related* or *not related*, but there is no standard nomenclature.[13] All spontaneous reports have an implied causal relationship as per regulatory guidance, regardless of the reporter's assessment.

The registry may use forms such as a structured questionnaire or an AE case report form to collect the information from providers or patients. When solicitation of AEs is not prespecified in the registry's operating plans, the registry may permit AE detection by asking general questions to solicit events, such as "Have you had any problems since your last visit or since we last spoke?" and then following up any such reports with probes as to what happened, diagnoses, and other documentation. This practice is not required.

3. Collecting AE Data in a Registry

There are two key considerations regarding AE collection as part of a registry: (1) what data need to be collected to meet the registry's safety-related objectives, and (2) what processes need to be in place to ensure that the registry is in compliance with regulations regarding expedited and periodic AE event reporting, if applicable. The data fields needed for the purpose of analysis by the registry may be minimal (e.g., event and onset date), whereas a complete SAE form for a subset of events reported to the registry

may be sought to fulfill the sponsor's reporting requirements. Due to the nature of registries, the goal of collecting enough data to meet the registry's objectives must constantly be balanced with the burden on sites. To this end, the processes for AE reporting should be streamlined as much as possible.

The collection of AE data by a registry is generally either intentionally solicited (meaning that the data are part of the uniform collection of information in the registry) or unsolicited (meaning that the AE information is volunteered or noted in an unsolicited manner and not as a required data element through a case report form). As described further below, it is good practice for a registry to specify when and how AE information (and any other events of special interest) should and should not be solicited from patients by a site and, if that information has been obtained, how and when the site should inform the appropriate persons.

While an AE may be reported to the manufacturer, to FDA (e.g., via MedWatch), or to the registry itself (and then from the registry to the manufacturer), it is strongly encouraged that the protocol describe the procedures that should be followed, and that the sites be trained in these procedures as well as in their general obligations and the relevant public health considerations. A separate safety reporting plan that fully identifies the responsible parties and describes the operational considerations may also be considered to ensure that potentially reportable information is evaluated in an appropriate timeframe, and, for manufacturer-sponsored registries, in accordance with any applicable standard operating procedures. This type of plan should also describe how deviations or systemic failures in detection and reporting processes will be identified, addressed, and considered for corrective action.

Determining whether a registry should use a case report form to collect AEs should be based on the principles described in Chapter 4, which refer to the scientific importance of the information for evaluating the specified outcomes of interest. This may mean that all, some, or no AEs are collected on the case report forms. However, if some AEs are collected in an intentional, solicited manner (e.g., routine collection of a primary or secondary outcome via an AE case report form) and others come to the registry's attention in an unsolicited, "spontaneous" way (e.g., when an AE is reported in the course of a registry contact, such as a call to the sponsor or to registry support staff), then from a practical perspective it is even more important to have a clear process, so that AEs that require reporting are identified. In this scenario, one best practice that is often used in electronic registry studies is to have a notification sent promptly to the sponsor's safety group when a case report form is submitted that contains specific or potential information indicating that a serious AE has occurred. This process allows for rapid followup by the sponsor, as needed.

4. AE Reporting by the Registry

Once suspicion has been aroused that an unexpected serious event has a reasonable possibility of being causally related to a drug, the AE should be reported to FDA through MedWatch, to the company that manufactures the product, or to the registry coordinating center. (See Chapter 11) A system should be developed such that all appropriate events are captured and duplicate reporting is avoided to the extent possible. Generally, AE reports are submitted directly by the site or by the registry to the manufacturer, since they are often most efficient at evaluating, processing, and reporting for regulatory purposes within the required time periods. Alternatively, sites could be instructed to report AEs directly to FDA, according to their normal practices for marketed products; however, this often means that the companies are not notified of the AE and are not able to followup or evaluate the event in the context of their safety

database. In fact, companies are not necessarily notified by FDA if an AE report comes directly to FDA, since only certain reports are shared with industry, and reporters have an option to request that the information not be shared directly with the company.[14] When sites report AEs directly to FDA, this process can also risk inadvertent duplication of information for events recorded both by the registry and the company.

Systematic collection of all AEs provides a unique resource of consistent and contemporaneously collected comparison information that can be used at a later date to conduct epidemiologic assessments. Ideally, the practice for handling AEs and SAEs should be applied to all treatments (including comparators) recorded in the registry, so that all subjects are treated similarly. In fact, a strong advantage of registries with systematic data collection and internal comparators is that they provide both numerators and denominators for safety events; thus, reporting of comparative known AE rates in the context of a safety evaluation provides valuable information on real-world performance. The contrast with comparators helps to promote clarity about whether the observed effects are unique to the product, unique to a class, or are common to the condition being treated. Reporting AEs without denominator information is less useful from a surveillance perspective since events rates cannot be calculated without both numerators and denominators. The reliability of the denominator should always be judged, however, by considering the likelihood that all events were reported appropriately.

For postapproval registries that are not financially supported by pharmaceutical companies, health care providers at registry sites should be instructed that if they suspect or otherwise become aware of a serious AE that has a reasonable possibility of being causally related to a drug or product, they should report the event directly to the product manufacturer (who must then report to FDA under regulation) or to FDA's MedWatch program (or local health authority if the study is conducted outside of the United States). Reporting can be facilitated by providing the MedWatch Form 3500,[15] information regarding the process for submission, and MedWatch contact information.

For registries that are sponsored or financially supported in full or in part by a regulated industry and that study a single product, the most efficient monitoring system to avoid duplicate reporting is one in which all physicians participating in the registry report all AEs (or SAEs only) directly to the sponsor or centralized designated responsible personnel, who then reports to the regulatory authorities. However, when products other than those exclusively manufactured by the sponsor are involved, including other treatments, sponsors will need to determine how to process AE reports that are received for these other products. Since sponsors are not obligated to report AEs for their competitors, it is good practice from a public health perspective to specify how the site should address those AEs (e.g., whether to report directly to the other product's manufacturer or to FDA). Options for the sponsor include (1) recommending that sites report the AEs of comparators directly to the manufacturer or to FDA; (2) collecting all AEs and forwarding the AE report directly to the comparator's manufacturer (who would then, in turn, report to FDA); and (3) actually reporting the AE for the comparator product directly to FDA. As standard practice in pharmacovigilance, many sponsors report events potentially associated with another manufacturer's drug to that manufacturer's safety department as a courtesy, rather than report events directly to FDA, and choose to continue that practice when conducting a registry or other observational study.

Some disease registries are not focused on a specific product, but rather on conducting natural history studies or evaluating treatment patterns and outcomes in a particular patient population prior to marketing

approval of the sponsor's product. In these situations, it is recommended that sites follow their own standard practices for spontaneous AE reporting, including reporting any events associated with a product known to be manufactured by the sponsor.

In most circumstances where a serious drug-associated AE is suspected, sites are encouraged to submit supportive data to sponsors, such as laboratory values, vital signs, and examination results, along with the SAE report form. If the event is determined to be an AE, the sponsor will include it in the safety database, evaluate it internally, and transfer the AE report to the regulatory authorities if required. It should be noted that the regulations represent minimum requirements for compliance; special circumstances for a particular product may result in additional events being reportable (e.g., expected events of particular interest to regulators). It should not be expected that registry participants be aware of all the reporting nuances associated with a particular product. To the extent possible, guidance on reporting events of special interest should be provided in the protocol and in any safety training.

If a registry is being managed by an external party, SAEs should be submitted to the sponsors as quickly as possible after the registry becomes aware of the event. In this situation, the registry is an agent of the sponsor, and FDA's 15-calendar-day reporting requirement starts as soon as the event has come to the attention of the registry. (See Section 7 below.) This submission can be accomplished by phone or fax, or by means of automated rules built into the vehicle used for data collection (such as automatic triggers that can be designed into electronic data capture programs). For direct regulatory submissions, the MedWatch Form 3500A[15] should be used for postapproval reporting for drugs and therapeutic biologics unless other means of submission are agreed upon. For vaccines, the Vaccine Adverse Event Reporting System (VAERS) should be consulted.[16] Foreign events may be submitted on a CIOMS form (the World Health Organization's Council for International Organizations of Medical Sciences),8 [17] [18] or a letter can be generated that includes the relevant information in narrative format.

5. Coding

Coding AEs into a standard nomenclature should be done by trained experts to assure accuracy and consistency. Reporters, patients, health care providers, and registry personnel should do their best to capture the primary data clearly, completely, and in as "natural" clinical language as possible. Since reporters may use different verbatim terms to describe the same event, it is recommended that sponsors apply coding conventions to code the verbatim terms. The Medical Dictionary for Regulatory Activities (MedDRA®) is customarily used throughout the product development cycle and as part of pharmacovigilance; however, other coding systems are also used. For example, SNOMED-CT (Systematized Nomenclature of Medicine-Clinical Terms) is used instead of MedDRA in some electronic health records. Coding the different verbatim language to preferred terms allows similar events to be appropriately grouped, creates consistency among the terms for evaluation, and maximizes the likelihood that safety signals will be detected.

Sponsors or their designees should review the accuracy of the coding of verbatim AEs into appropriate terms. If coding is performed by someone other than the sponsor, any applicable coding conventions associated with the underlying condition or product should be shared. Review of the coding process should focus on the use of terms that do not accurately communicate the severity or magnitude of the AE or possibly mischaracterize the AE. Review of the coded terms compared with reported verbatim terms should be performed in order to ensure consistency and accuracy of the AE reporting and to minimize

variability of coding of similar AE terms. Attention to consistency is especially important, as many different individuals may code AEs over time, and this situation contributes to variability in the coding process. In addition to monitoring AEs individually for complete clinical evaluation of the safety data, sponsors should consider grouping and analyzing clinically relevant coded terms that could represent similar toxicities or syndromes. Combining terms may provide a method of detecting less common and serious events that would otherwise be obscured. However, sponsors should be careful when combining related terms to avoid amplifying a weak signal or obscuring important overall findings when grouping is overly broad. In addition to monitoring individual AEs, sites and registry personnel should be attentive to toxicities that may cluster into syndromes.

6. Adverse Event Management

In some cases, such as when a safety registry is created as a condition of regulatory approval, a data safety monitoring board (DSMB), data monitoring committee (DMC), or adjudication committee may be established with the primary role of periodically reviewing the data as they are generated by the registry. Such activities are generally discussed directly with the regulatory authorities, such as FDA. These authorities are typically involved in the design and critique of protocols for postapproval studies. Ultimately, registry planning and the registry protocol should anticipate and clearly delineate the roles, responsibilities, processes, forms, and lines of communication for AE reporting for sites, registry personnel, the DSMB or adjudication committee if one exists, and the sponsoring organization. Documentation should be provided for definitions and approaches to determining what is considered unexpected and possibly related to drug or device exposure. The management of AE reporting should be clearly specified in the registry protocol, including explanations of the roles, responsibilities, processes, and methods for handling AE reports by the various parties conducting the registry, and for performing followup activities with the site to ensure that complete information is obtained. Sponsors who are stakeholders in a registry should have a representative of their internal drug safety or pharmacovigilance group participate in the design and review of the registry protocol and have a role in the data collection and reporting process (discussed in Chapter 2) to facilitate appropriate and timely reporting and communication.

For postapproval studies financially sponsored by manufacturers, the overall company AE monitoring systems are usually operated by personnel experienced in drug safety (also referred to as pharmacovigilance, regulatory safety, product safety, and safety and risk management). If sites need to report or discuss an AE, they can call the contact number provided for the registry, and are then prompted to press a number if reporting an AE. This number then transfers them to drug safety surveillance so that they can interact directly with personnel in this division and bypass the registry coordinating group. These calls may or may not be tracked by the registry. Alternatively, the registry system can provide instructions to the site on how to report AEs directly to the sponsor's drug safety surveillance division. By this method, the sponsor provides a separate contact number for AE reporting (independent of the registry support staff) that places the site in direct contact with drug safety personnel. This process minimizes the possibility of duplicate AE reports and the potentially complicated reconciliation of two different systems collecting AE information. Use of this process is critical when dealing with products that are available via a registry system as well as outside of a registry system, and it allows sites to have one designated drug safety representative for interaction.

Sponsors of registries designed specifically for surveillance of product safety are strongly encouraged to hold discussions with the regulatory authorities when considering the design of the AE monitoring system. These discussions should be focused on the purpose of the registry, the "best fit" model for AE monitoring, and the timing of routine registry updates. With respect to internal operations chosen by the sponsor to support the requirements of an AE monitoring system, anecdotal feedback suggests that health authorities expect compliance with the agreed-upon requirements. Details regarding implementation are the responsibility of the sponsor.

It should also be noted that FDA's Proposed Rule for Safety Reporting Requirements for Human Drug and Biologics Products (68 FR 12406, March 14, 2003) suggests that the responsible point of contact for FDA should be provided for all expedited and periodic AE reports, and preferably, this individual should be a licensed physician. Although this proposed rule has never been finalized, the principle is similar to the Qualified Person for Pharmacovigilance (QPPV) in Europe, whereby a specific, qualified individual is identified to provide responses to health authorities, upon request, including those regarding AEs reported via the registry system. Updated pharmacovigilance regulations issued by the European Medicines Agency (EMA) are expected to be implemented in July 2012.[19,20]

7. Adverse Event Required Reporting for Registry Sponsors

The reporting requirements of the sponsor directly affect how registries should collect and report AEs. Sponsors that are regulated industries are subject to the requirements shown in Table 16. ICH guidelines describe standards for expedited reporting5 [21] and provide recommendations for periodic safety update reports[22] that are generally accepted globally.

Table 16. Overview of Serious Adverse Event Reporting Requirements for Marketed Products

Type of requirement	Drug and Biologics	Devices
U.S. postmarketing regulations	Primary: 21 CFR 314.80 (drugs), 21 CFR 600.80 (biologics) Other: 21 CFR 310.305, 21 CFR 314.98	21 CFR 803.20
Required reporting source	Regulated industries	Manufacturer, importer, user facility
Required reports	Serious, unexpected, and with a reasonable possibility of being related to drug exposure (with some exceptions)	Death or serious injury; device malfunction
Alternative reports	Not applicable	Summary reports (periodic line-listing of reports of well-known events)
Timeframe for reporting	15 calendar days for expedited reports	5 workdays, 10 workdays, or 30 calendar days, depending on the source and action required
Standard reporting form	MedWatch 3500A (for mandatory reporting required of a regulated industry) MedWatch 3500 (for voluntary reporting by health care professionals, consumers, and patients)	
Web sites	www.fda.gov/medwatch	www.fda.gov/cdrh/mdr

Requirements for regulated industries that sponsor or financially support a registry include expedited reporting of serious and unexpected AEs made known to them via spontaneous reports. For registries, the 15-calendar-day notification applies if the regulated industry believes there is a reasonable possibility that the unexpected SAE was causally related to product exposure. Best practices for international reporting are that all "affiliates" of a sponsor report serious, unexpected, and possibly related events to the sponsor in a timely fashion, ideally within 2 calendar days; this allows the sponsor, in turn, to complete notification to the responsible regulatory authority within a total of 15 calendar days. Events that do not meet the requirements of expedited reporting (such as nonserious events or serious events considered expected or not related) may require submission through inclusion in an appropriate safety update, such as the New Drug Application (NDA) or Biologic Licensing Application (BLA) Annual Report, Periodic Report, or Periodic Safety Update Report (PSUR), as applicable.4 In many cases, sponsors are also required to provide registry safety updates to the health authority. Thus, sponsors may coordinate registry safety updates (i.e., determining the date for creating the dataset—the data cutoff date) with the timing of the NDA Annual Report, Periodic Report, PSUR, or other agreed-upon periodic reporting format. Devices, however, have different reporting requirements (see www.fda.gov/cdrh/mdr). In any event, sponsors should discuss safety reporting requirements for their specific registries with the applicable health authorities (such as FDA and European Medicines Agency [EMA]) before finalizing their registry protocol.

In some cases, a registry sponsor may encourage sites to systematically report all potential SAEs to the sponsor. Given the potential for various assessments by different sites of the seriousness and relatedness of a particular AE—and therefore, inconsistency across sites in the evaluation of a particular AE—this method has certain advantages. In addition, expectedness is not always a straightforward assessment, and the expectedness of events can have significant variability depending on the local approved product labeling. For this reason, it is important that this determination be made by the sponsor and not the reporter of the event. Although this approach may result in substantially greater demands on the sponsor to evaluate all reports, it helps ensure compliance and avoid underreporting, to the extent possible. Furthermore, sponsors must make their own assessments regarding the causality of individual solicited events. This requirement typically does not affect the need for reporting, but allows the sponsor to provide its own evaluation in the full context of the safety database. For these reasons, planning for high-quality and consistent training in AE reporting requirements across sites is the preferred approach for a patient registry.

Regardless of who assesses presumed relatedness, sponsors should be prepared to manage the increased volume of AE reports, and sponsors' registry staff should be trained to understand company policy and regulations on AE reporting in order to ensure compliance with local regulations. This training includes the ability to identify and evaluate the attributes of each AE and determine whether the AE should be reported to the health authority in keeping with local regulation. Sponsors are encouraged to appoint a health care practitioner to this role in order to ensure appropriate assessment of the characteristics of an AE.

When biopharmaceutical or device companies are not sponsoring, financially supporting, or participating in a registry in any way, AE reporting is dependent upon the "become aware" principle. If any agent or employee of the company receives information regarding an AE report, the agent or employee must

document receipt and comply with internal company policy and regulatory requirements regarding AE reporting, to assure compliance with applicable drug and device regulations.

8. Special Case: Risk Evaluation and Mitigation Strategies (REMS)

Under FDAAA (2007), FDA established a legally enforceable new framework for risk management of products with known safety concerns, called Risk Evaluation and Mitigation Strategies (REMS).6 [23] [24] The purpose of REMS is to ensure that the benefits of a particular drug outweigh the risks. New REMS programs can be imposed by FDA during clinical development, as part of the approval process, or at any time post approval, should a new safety signal be identified. Although each REMS is customized depending on the product and associated safety issues, potential components include some combination of:

- A medication guide and/or patient package insert. Medication guides are informational packets distributed with some prescription drugs, which provide important information to patients about possible side effects and drug-drug interactions. The FDA has clarified in which situations a medication guide is required to be available and distributed to patients.[25] A medication guide alone can and frequently does constitute a REMS.
- A communication plan that specifies targeted education and outreach for physicians, pharmacists, and patients.
- Elements to assure safe use (ETASU), in some cases. ETASU may include restriction of prescribing to health care providers with particular training, experience, and certification; dispensing of the drug in restricted settings; documentation of safe use conditions (such as laboratory results or specific patient monitoring); and registries.[24]

Unlike the less structured disease or exposure registries discussed above, a restricted-access system associated with an ETASU is designed for approved products that have particular risk-benefit profiles that require more careful controls. The purpose of ETASU is to mitigate a certain known drug-associated risk by ensuring that product access is tightly linked to some preventive and/or monitoring measure. Examples include systems that monitor laboratory values, such as white blood cell counts during clozapine administration to prevent severe leucopenia, or routine pregnancy testing during thalidomide administration to prevent in utero exposure of this known teratogenic compound. When these programs include registries, the registries often prospectively collect a battery of information using standardized instruments.

Data collection under ETASU may carry special AE reporting requirements, and as a result of the extensive contact with a variety of potential sources of safety information (e.g., pharmacists and patients), care should be taken to identify all possible routes of reporting. If special requirements exist, they should be made explicit in the registry protocol, with clear definitions of roles, responsibilities, and processes. Training of involved health care providers, such as physicians, nurses, and pharmacists, can be undertaken with written instructions, via telephone or with face-to-face counseling. Training of these health care providers should also extend beyond AE reporting to the specific requirements of the program in question. Such training may include the intended use and associated risk of the product, appropriate patient enrollment, and specific patient monitoring requirements, including guidelines for product discontinuation and management of AEs, as well as topics to cover during comprehensive counseling of patients. The objectives of the ETASU system and overall REMS should be clearly stated (e.g.,

prevention of in utero exposure during therapy via routine pregnancy testing), and registration forms that document the physician's and pharmacist's attestation of their commitment to requirements of the patient registry system should be completed prior to prescribing or dispensing the product.

9. Reporting Breaches of Confidentiality or Other Risks

In addition to addressing regulatory responsibilities for reporting adverse events, registries must also understand regulatory and ethical requirements and expectations regarding breaches of confidentiality or the reporting of other risks to patients that may arise during the course of a registry. The Health Information Technology for Economic and Clinical Health Act (HITECH Act) requires HIPAA (Health Insurance Portability and Accountability Act of 1996) covered entities and their business associates to provide notification following a breach of unsecured protected health information.[26] See Chapter 7 for a detailed discussion of the HITECH Act.

Beyond this regulation, registries should establish clear notification procedures for breaches of confidentiality or other risks that become known during the course of the registry whether or not they are governed by HIPAA.

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Chapter 13. Analysis, Interpretation, and Reporting of Registry Data To Evaluate Outcomes

1. Introduction

Registries have the potential to produce databases that are an important source of information regarding health care patterns, decisionmaking, and delivery, and their subsequent association with patient outcomes. Registries, for example, can provide valuable insight into the safety and/or effectiveness of an intervention or the efficiency, timeliness, quality, and patient-centeredness of a health care system. The utility and applicability of registry data rely heavily on the quality of the data analysis plan and its users' ability to interpret the results. Analysis and interpretation of registry data begin with a series of core questions:

- *Study purpose*: Were the objectives/hypotheses predefined or post hoc?
- *Patient population*: Who was studied?
- *Data quality*: How were the data collected, reviewed, and verified?
- *Data completeness*: How were missing data handled?
- *Data analysis*: How were the analyses chosen and performed?

While registry data present many opportunities for meaningful analysis, there are inherent challenges to making appropriate inferences. A principal concern with registries is that of making inferences without regard to the quality of data, since quality standards have not been previously well established or consistently reported. In some registries, comparison groups may not be robustly defined, and information provided about the external validity of a registry sample is often limited. These factors must be considered when making inferences based on analyses of registry data.[1]

This chapter explains how analysis plans are constructed for registries, how they differ depending on the registry's purpose, and how registry design and conduct can affect analysis and interpretation. The analytic techniques generally used for registry data are presented, addressing how conclusions may be drawn from the data and what caveats are appropriate. The chapter also describes how timelines for data analysis can be built in at registry inception and how to determine when the registry data are complete enough to begin analysis.

2. Hypotheses and Purposes of the Registry

While it may be relatively straightforward to develop hypotheses for registries intended to evaluate safety and effectiveness, not all registries have specific, testable, or simple hypotheses. Disease registries commonly have aims that are primarily descriptive, such as describing the typical clinical features of individuals with a disease, variations in phenotype, and the clinical progression of the disease over time (i.e., natural history). These registries play a particularly important role in the study of rare diseases.

In the case of registries where the aim is to study the associations between specific exposures and outcomes, prespecification of the study methodology and presence or absence of a priori hypotheses or research questions may affect the acceptance of results of studies derived from registry data. The many possible scenarios are well illustrated by examples at the theoretical extremes.

On one extreme, a study may evolve out of a clear and explicit prespecified research question and hypothesis. In such a study, there may have been preliminary scientific work that laid the conceptual foundation and plausibility for the proposed study. The investigators fully articulate the objectives and analytic plan before embarking on any analysis. The outcome is clearly defined and the statistical approach documented. Secondary analyses are identified and may be highlighted as hypothesis generating. The investigators have no prior knowledge of analyses in this database that would bias them in the formulation of their study objective. The study is conducted and published regardless of the result. The paper states clearly that the objective and hypothesis were prespecified. For registries that are intended to support national coverage determinations with data collection as a condition of coverage, the specific coverage decision question may be specified a priori as the research question in lieu of a formal hypothesis.

At the other extreme, a study may evolve out of an unexpected observation in a database in the course of doing analyses for another purpose. A study could also evolve from a concerted effort to discover associations—for example, as part of a large effort to understand disease causation. In such a study, the foundation for the study is developed post hoc, or after making the observation. Because of the way in which the observation was found, the rationale for the study is developed retrospectively. The paper publishing this study's results does not clearly state that the objective and hypothesis were not prespecified.

Of course, there are many examples that fall between these extremes. An investigator may suspect an association for many variables but find the relationship for only one of them. The investigator decides to pursue only the positive finding and develop a rationale for a study or grant. The association was sought, but it was sought along with associations for many other variables and outcomes.

Thus, while there is substantial debate about the importance of prespecified hypotheses,[2,3] there is general agreement that it is informative to reveal how the study was developed. Transparency in methods is needed so that readers may know whether these studies are the result of hypotheses developed independently of the study database, or whether the question and analyses evolved from experience with the database and multiple iterations of exploratory analyses. Both types of studies have value.

3. Patient Population

The purpose of a registry is to provide information about a specific patient population to which all study results are meant to apply. To determine how well the study results apply to the target population, five populations, each of which is a subset of the preceding population, need to be considered, along with how well each population represents the preceding population. These five subpopulations are shown in Figure 5.

The *target population* is defined by the study's purpose. To assess the appropriateness of the target population, one must ask the question, Is this really the population that we need to know about? For example, the target population for a registry of oral contraceptive users would include women of childbearing age who could become pregnant and are seeking to prevent pregnancy. Studies often miss important segments of the population in an effort to make the study population more homogeneous. For example, it is less informative than desirable if a study to assess a medical device used to treat patients for cardiac arrhythmias defines only men as its target population, because the device is designed for use in both men and women.

The *accessible population* is defined using inclusion criteria and exclusion criteria. The inclusion criteria define the population that will be used for the study and generally include geographic (e.g., hospitals or clinics in the New England region), demographic, disease-specific, and temporal (e.g., specification of the included dates of hospital or clinic admission), as well as other criteria. Conversely, the exclusion criteria seek to eliminate specific patients from study and may be driven by an effort to assure an adequate-sized population of interest for analysis. The same goals may be said of inclusion criteria, since it is difficult to separate inclusion from exclusion criteria (e.g., inclusion of adults aged 18 and over vs. exclusion of children under age 18).

The accessible population may lose representativeness to the extent that convenience plays a part in its determination, because people who are easy to enroll in the registry may differ in some critical respects from the population at large. Similarly, to the extent that homogeneity plays a part in determining the accessible population, it is less likely to be representative of the entire population because certain population subgroups will be excluded.

Factors to be considered in assessing the accessible population's representativeness of the target population include all the inclusion and exclusion criteria mentioned above. One method of evaluating representativeness is to describe the demographics and other key descriptors of the registry study population and to contrast its composition with patients with similar characteristics who are identified from an external database, such as might be obtained from health insurers, health maintenance organizations, and the U.S. Surveillance Epidemiology and End Results (SEER) cancer registries.[4]

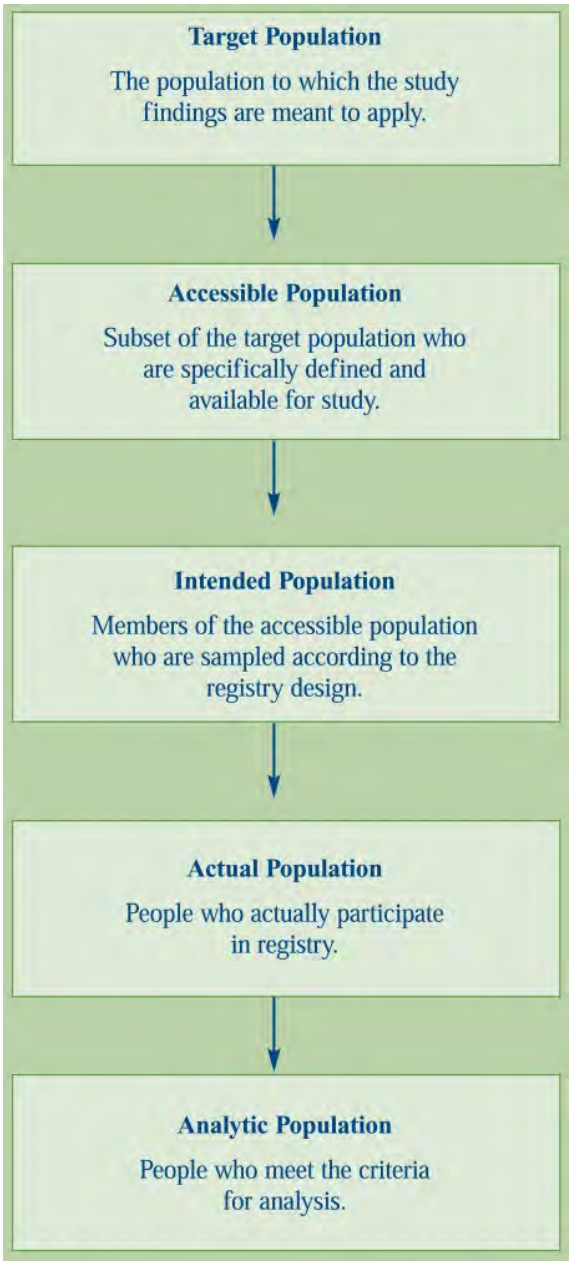
However, simple numerical/statistical representativeness is not the main issue. Representativeness should be evaluated in the context of the purpose of the study—that is, whether the study results can reasonably be generalized or extrapolated to other populations of interest outside of those included in the accessible population. (See Case Example 23.) For example, suppose that the purpose of the study is to assess the effectiveness of a drug in U.S. residents with diabetes. If the accessible population includes no children, then the study results may very well not apply to children, since children often metabolize drugs very differently than adults.

On the other hand, consider the possibility that the accessible population is generally drawn from a geographically isolated region, whereas the target population may be the entire United States or the world. In that case, the accessible population is not geographically representative of the target population, but that circumstance would have little or no impact on the representativeness of the study findings to the target population if the action of the drug (or its delivery) does not vary geographically (which we would generally expect to be the case, unless pertinent racial/genetic or dietary factors were involved). Therefore, in this example, the lack of geographical representativeness would not affect interpretation of results.

The reason for using an *intended population* rather than the whole accessible population for the study is simply a matter of convenience and practicality. The issues to consider in assessing how well the intended population represents the accessible population are similar to those for assessing how well the accessible population represents the target population. The main difference is that the intended population may be specified by a sampling scheme, which often tries to strike a balance among representativeness, convenience, and budget. If the intended population is a random sample of the accessible population, it may be reasonably assumed that it will represent the accessible population; however, for many, if not

most, registries, a complete roster of the accessible population does not exist. More commonly, the intended population is compared with the accessible population in terms of pertinent variables.

Figure 5. Patient Populations



To the extent that convenience or other design (e.g., stratified random sample) is used to choose the intended population, one must consider the extent to which the sampling of the accessible population—by means other than random sampling—has decreased the representativeness of the intended population. For example, suppose that, for the sake of convenience, only patients who attend clinic on Mondays are included in the study. If patients who attend clinic on Mondays are similar in every relevant respect to other patients, that may not constitute a limitation. But if Monday patients are substantially different from patients who attend clinic on other days of the week (e.g., well-baby clinics are held on Mondays) and if

those differences affect the outcome that is being studied (e.g., proportion of baby visits for "well babies"), then that sampling strategy would substantially alter the interpretations from the registry and would be considered a meaningful limitation.

The extent to which the *actual population* is not fully representative of the intended population is generally a matter of real-world issues that prevent the initial inclusion of study subjects or adequate followup. In assessing representativeness, one must consider the likely underlying factors that caused those subjects not to be included in the analysis of study results and how that might affect the interpretations from the registry. For example, consider a study of a newly-introduced medication, such as an antiinflammatory drug that is thought to be as effective as other products and to have fewer side effects but that is more costly. Inclusion in the actual population may be influenced by prescribing practices governed by a health insurer (such as the new drug being approved for reimbursement only for patients who have "failed" treatment with other antiinflammatory products, resulting in an actual population that is systematically different from the target population of potential antiinflammatory drug users). The actual population may be refractory to treatment or have more comorbidities (e.g., gastrointestinal problems), and may be specifically selected for treatment beyond the intention of the study-specified inclusion criteria. In fact, registries of newly-introduced drugs and devices may often include patients who are different from the ultimate target population.

Finally, the *analytic population* includes all those patients who meet the criteria for analysis. In some cases, it becomes apparent that there are too few cases of a particular type or patients with certain attributes, such that these subgroups do not contribute enough information for meaningful analysis. Patients may also be excluded from the analysis population because their conditions are so rare that to include them could be considered a breach of patient confidentiality. Analytic populations are also created to meet specific needs. For example, an investigator may request a dataset that will be used to analyze a subset of the registry population, such as those who had a specific treatment or condition.

A related issue is that of *early adopters*,[5] in which practitioners who are quick to use a novel health care intervention or therapy differ from those who use it only once it is well established. For example, a registry of the use of a new surgical technique may initially enroll largely academic physicians and only much later enroll community-based surgeons. If the outcomes of the technique differ between the academic surgeons (early adopters) and community-based surgeons (later adopters), then the initial results of the registry may not reflect the true effectiveness of the technique in widespread use. Patients selected for treatment with a novel therapy may also differ with regard to factors such as severity or duration of disease and prior treatment history, including treatment failures. (For example, patients with more severe or late-stage disease who have failed other treatments might be more likely to use a newly-approved product that has shown efficacy in treating their condition soon after approval.) Later on, patients with less severe disease may start using the product.

Finally, patients who are included in the analytic population for a given analysis of registry data may also be subject to selection or inclusion criteria (admissibility criteria), and these may affect interpretation of the resulting analyses. (See Chapter 18.) One example is including only patients who remain enrolled and attend followup visits through two years after study initiation in an analysis of adherence to therapy; it is possible or likely that adherence will be different among those who remain enrolled in the study and have multiple followup visits than those who do not. Differential loss to followup, whereby patients who are

lost may be more likely to experience adverse outcomes, such as mortality, than those who remain under observation, is a related issue that may lead to biased results. (See Chapter 3.)

4. Data Quality Issues

In addition to a full understanding of study design and methodology, analysis of registry events and outcomes requires an assessment of data quality. One must consider whether most or all important covariates were collected, whether the data were complete, and whether missing data were handled appropriately, as well as whether the data are accurate.

4.1. Collection of All Important Covariates

While registries are generally constructed for a particular purpose or purposes, registry information may be collected for one purpose (e.g., provider performance feedback) and then used for another (e.g., addressing a specific clinical research question). When using an available database for additional purposes, one needs to be sure that all the information necessary to address a specific research question was collected in a manner that is sufficient to answer the question.

For example, suppose the research question addresses the comparative effectiveness of two treatments for a given disease using an existing registry. To be meaningful, the registry should have accurate, well-defined, and complete information, including potential confounding and effect modifying factors; population characteristics of those with the specified disease; exposures (whether patients received treatment A or B); and patient outcomes of interest. Confounding factors are variables that influence both the exposure (treatment selection) and the outcome in the analyses. These factors can include patient factors (age, gender, race, socioeconomic factors, disease severity, or comorbid illness); provider factors (experience, skills); and system factors (type of care setting, quality of care, or regional effects). While it is not possible to identify all confounding factors in planning a registry, it is desirable to give serious thought to what will be important and how the necessary data can be collected. While effect modification is not a threat to validity, it is important to consider potential effect modifiers for data collection and analysis in order to evaluate whether an association varies within specific subgroups.[6] Analysis of registries requires information about such variables so that the confounding covariates can be accounted for, using one of several analytic techniques covered in upcoming sections of this chapter. In addition, as described in Chapter 3, eligibility for entry into the registry may be restricted to individuals within a certain range of values for potential confounding factors in order to reduce the effects of these factors. Such restrictions may also affect the generalizability of the registry.

4.2. Data Completeness

Assuming a registry has the necessary data elements, the next step is to ensure that the data are complete. Missing data can be a challenge for any registry-based analysis. Missing data include situations where a variable is directly reported as missing or unavailable, where a variable is "nonreported" (i.e., the observation is blank), where the reported data may not be interpretable, or where the value must be imputed to be missing because of data inconsistency or out-of-range results. Before analyzing a registry database, the database should be "cleaned" (discussed in Chapter 11.2.5.), and attempts should be made to obtain as much missing data as realistically possible from source documents. Inconsistent data (e.g., answer yes to a question at one point and no to the same question at another) and out-of-range data (a 500-year-old patient) should be corrected when possible. Finally, the degree of data completeness should

be summarized for the researcher and eventual consumer of analyses from the registry. Detailed examples of sources of incomplete data are described in Chapter 18.

4.3. Missing Data

The intent of any analysis is to make valid inferences from the data. Missing data can threaten this goal by both reducing the information yield of the study and, in many cases, introducing bias. A thorough review of types of missing data with examples can be found in Chapter 18. Briefly, the first step is to understand which data are missing. The second step is to understand why the data are missing (e.g., missing item-response or right censoring). Finally, missing data fall into three classic categories of randomness.[7]

- *Missing completely at random (MCAR)*: Instances where there are no differences between subjects with missing data and those with complete data. In such random instances, missing data only reduce study power without introducing bias.
- *Missing at random (MAR)*: Instances where missing data depend on known or observed values but not unmeasured data. In such cases, accounting for these known factors in the analysis will produce unbiased results.
- *Missing not at random (MNAR)*: Here, missing data depend on events or factors not measured by the researcher and thus potentially introduce bias.

To gain insight into which of the three categories of missing data are in play, one can compare the distribution of observed variables for patients with specific missing data to the distribution of those variables for patients for whom those same data are present.

While pragmatically it is difficult to determine whether data are MCAR or MAR, there are, nonetheless, several means of managing missing data within an analysis. For example, a *complete case* strategy limits the analysis to patients with complete information for all variables. This is the default strategy used in many standard analytic packages (e.g., SAS, Cary, NC). A simple deletion of all incomplete observations, however, is not appropriate or efficient in all circumstances, and it may introduce significant bias if the deleted cases are substantively different from the retained, complete cases (i.e., not MCAR). In observational studies with prospective, structured data collection, missing data are not uncommon, and the complete case strategy is inefficient and not generally used. For example, patients with diabetes who were hospitalized because of inadequate glucose control might not return for a scheduled followup visit at which HbA1c was to be measured. Those missing values for HbA1c would probably differ from the measured values because of the reason for which they were missing, and they would be categorized as MNAR. In an example of MAR, the availability of the results of certain tests or measurements may depend on what is covered by patients' health insurance (a known value), since registries do not typically pay for testing. Patients without this particular measurement may still contribute meaningfully to the analysis. In order to include patients with missing data, one of several imputation techniques may be used to estimate the missing data.

Imputation is a common strategy in which average values are substituted for missing data using strategies such as *unconditional* and *conditional mean, multiple hot-deck*, and *expectation maximum*, among others.[7,8] For data that are captured at multiple time points or repeated measures, investigators often "carry forward" a last observation. However, such a technique can be problematic if early dropouts occur and a response variable is expected to change over time or when the effect of the exposure (or treatment) is intermittent. *Worst-case* imputation is another means of substitution in which investigators test the

sensitivity of a finding by substituting a worst-case value for all missing results. While this is conservative, it offers a *lower bound* to an association rather than an accurate assessment. One particular imputation method that has received significant attention in recent analyses has been termed *multiple imputation*. Rubin first proposed the idea to impute more than one value for a missing variable as a means of reflecting the uncertainty around this value.[9] The general strategy is to replace a missing value with multiple values from an approximate distribution for missing values. This produces multiple complete datasets for analysis from which a single summary finding is estimated.

There are several issues concerning how prognostic models for decisionmaking can be influenced by data completeness and missing data.[10] Burton and Altman reviewed 100 multivariable cancer prognostic models published in seven leading cancer journals in 2002. They found that the proportion of complete cases was reported in only 39 studies, while the percentage missing for important prognostic variables was reported in 52 studies. Comparison of complete cases with incomplete cases was provided in 10 studies, and the methods used to handle missing data were summarized in 32 studies. The most common techniques used for handling missing data in this review article were (a) complete case analysis (12), (b) dropping variables with high numbers of missing cases from model consideration (6), and (c) using some simple author imputation rule (6). Only one study reported using multiple imputation. The reviewers concluded that there was room for improvement in the reporting and handling of missing data within registry studies.[10]

Readers interested in learning more about methods for handling missing data and the potential for bias are directed to other useful resources by Greenland and Finkle,[11] Hernán and colleagues,[12] and Lash, Fox, and Fink.[13]

It is important to keep in mind that the impact of data completeness will differ, depending on the extent of missing data and the intended use of the registry. It may be less problematic with regard to descriptive research than research that is intended to support decisionmaking. For all registries, it is important to have a strategy for how to identify and handle missing data as well as how to explicitly report on data completeness to facilitate interpretation of study results. For more information on other specific types of missing data issues (e.g., left truncation), please see Chapter 18.

4.4. Data Accuracy and Validation

While observational registry studies are usually not required to meet U.S. Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) standards of Good Clinical Practice developed for clinical trials, sponsors and contract research organizations that conduct registry studies are responsible for ensuring the accuracy of study data to the extent possible. Detailed plans for site monitoring, quality assurance, and data verification should be developed at the beginning of a study and adhered to throughout its lifespan. Chapter 11 discusses in detail approaches to data collection and quality assurance, including data management, site monitoring, and source data verification.

Ensuring the accuracy and validity of data and programming at the analysis stage requires additional consideration. The Office of Surveillance and Epidemiology (OSE) of FDA's Center for Drug Evaluation and Research uses the manual *Standards of Data Management and Analytic Process in the Office of Surveillance and Epidemiology* for analyses of databases conducted within OSE; the manual addresses many of these issues and may be consulted for further elaboration on these topics.[14] Topics addressed that pertain to ensuring the accuracy of data just prior to and during analysis include developing a clear

understanding of the data at the structural level of the database and variable attributes; creating analytic programs with careful documentation and an approach to variable creation and naming conventions that is straightforward and, when possible, consistent with the Clinical Data Interchange Standards Consortium (CDISC) initiative; and complete or partial verification of programming and analytic dataset creation by a second analyst.[14]

For detail about validation substudies, please see Chapter 18.

5. Data Analysis

This section provides an overview of practical considerations for analysis of data from a registry. As the name suggests, a descriptive study focuses on describing frequency and patterns of various elements of a patient population, whereas an analytical study focuses on examining associations between patients or treatment characteristics and health outcomes of interest (e.g., comparative effectiveness).

Statistical methods commonly used for descriptive purposes include those that summarize information from continuous variables (e.g., mean, median) or from categorical variables (e.g., proportions, rates). Registries may describe a population using incidence (the proportion of the population that develops the condition over a specified time interval) and prevalence (the proportion of the population that has the condition at a specific point in time). Another summary estimate that is often used is an incidence rate. The incidence rate (also known as absolute risk) takes into account both the number of people in a population who develop the outcome of interest and the person-time at risk, or the length of time contributed by all people during the period when they were in the population and the events were counted.

For studies that include patient followup, an important part of the description of study conduct is to characterize how many patients are "lost," or drop out, during the course of the registry, at what point they are lost, and if they return. Lasagna plots are one convenient method to visually assess missing data over time when conducting a longitudinal analysis.[15] Figure 6 illustrates key points of information that provide a useful description of losses to followup and study dropouts.

For analytical studies, the association between a risk factor and outcome may be expressed as attributable risk, relative risk, odds ratio, or hazard ratio, depending on the nature of the data collected, the duration of the study, and the frequency of the outcome. Attributable risk, a concept developed in the field of public health and preventive medicine, is defined as the proportion of disease incidence that can be attributed to a specific exposure, and it may be used to indicate the impact of a particular exposure at a population level. The standard textbooks cited here have detailed discussions regarding epidemiologic and statistical methods commonly used for the various analyses supported by registries.6[,16,17,18,19]

For analytical studies of data derived from observational studies such as registries, it is important to consider the role of confounding. Although those planning a study try to collect as much data as possible to address known confounders, there is always the chance that unknown confounders will affect the interpretation of analyses derived from observational studies. It is important to consider the extent to which bias (systematic error stemming from factors that are related to both the decision to treat and the outcomes of interest [confounders]) could have distorted the results. For example, selective prescribing (confounding by indication) results when people with more severe disease or those who have failed other treatments are more likely to receive newer treatments; these patients are systematically different from other patients who may be treated with the product under study. Misclassification in treatment can result

from the patient's incorrect recall of dose, or poor adherence or treatment compliance. Other types of bias include detection bias[20] (e.g., when comparison groups are assessed at different points in time or by different methods), selective loss to followup in which patients with the outcomes of most interest (e.g., sickest) may be more likely to drop out of one treatment group than another, and performance bias (e.g., systematic differences in care other than the intervention under study, such as a public health initiative promoting healthy lifestyles directed at patients who receive a particular class of treatment).

Confounding may be evaluated using stratified analysis, multivariable analysis, sensitivity analyses, and simple or quantitative bias analysis.[12] Appropriate methods should be used to adjust for confounding. For example, if an exposure or treatment varies over time and the confounding variable also varies over time, traditional adjustment using conventional multivariable modeling will introduce selection bias. Marginal structural models use inverse probability weighting to account for time-dependent confounding without introducing selection bias.[21] The extensive information and large sample sizes available in some registries also support use of more advanced modeling techniques for addressing confounding by indication, such as the use of propensity scores to create matched comparison groups, or for stratification or inclusion in multivariable risk modeling.[22,23,24,25] New methods also include high dimensional propensity score (hdPS) for adjustment using administrative data.[26] The uptake of these approaches in the medical literature in recent years has been extremely rapid, and their application to analyses of registry data has also been broad. Examples are too numerous for a few selections to be fully representative, but registries in nearly every therapeutic area, including cancer,[27] cardiac devices,[28] organ transplantation,[29] and rare diseases,[30] have published the results of analyses incorporating approaches based on propensity scores. As noted in Chapter 3, instrumental variable methods present opportunities for assessing and reducing the impact of confounding by indication,[31,32,33] but verification of the assumptions are important to ensure an instrument is valid.[34] Violations in the instrumental variable assumptions or the use of a weak instrument will lead to results more biased than those from conventional methods.[35] While a variety of methods have been developed to address confounding, particularly confounding by indication, residual confounding may still be present even after adjustment; therefore, these methods may not fully control for unmeasured confounding.[35] For specific examples of the application of these methods, please see Chapter 18. Information bias, such as misclassification, and selection bias are also threats to the validity of our findings and examples can be found in Chapter 18. For further information on how to quantify bias, please see Lash, Fox, and Fink.[13]

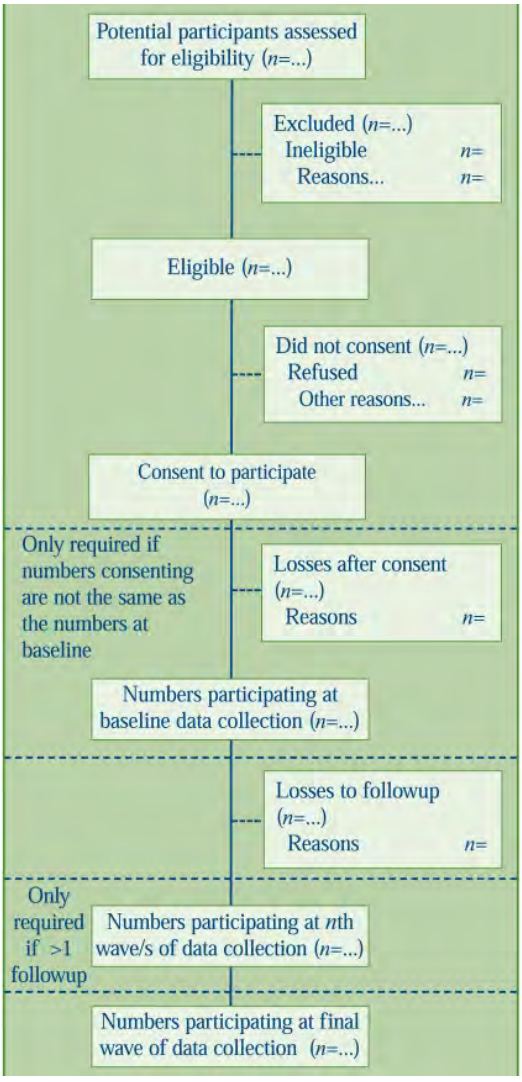
Groupings within a study population, such as patients seen by a single clinician or practice, residents of a neighborhood, or other "clusters," may themselves impact or predict health outcomes of interest. Such groupings may be accounted for in analysis through use of analytic methods including analysis of variance (ANOVA), and hierarchical or multilevel modeling.[36,37,38,39]

Heterogeneity of treatment effect (HTE) is also an important consideration for comparative effectiveness research as the effect of a treatment may vary within subgroups of heterogeneous patients.[40] Use of stratification on the propensity score has been used to identify HTE and may identify clinically meaningful differences between subgroups.

For economic analyses, the analytic approaches often encountered are cost-effectiveness analyses and cost-utility studies. To examine cost-effectiveness, costs are compared with clinical outcomes measured in units such as life expectancy or years of disease avoided.[41] Cost-utility analysis, a closely related

technique, compares costs with outcomes adjusted for quality of life (utility) using measures known as quality-adjusted life years (QALYs). Since most new interventions are more effective but also more expensive, another analytic approach examines the incremental cost-effectiveness ratio (ICER) and contrasts that to the willingness to pay. (Willingness-to-pay analyses are generally conducted on a country-by-country basis, since various factors relating to national health insurance practices and cultural issues affect willingness to pay.) The use of registries for cost-effectiveness evaluations is a fairly recent development, and consequently, the methods are evolving rapidly. More information about economic analyses can be found in standard textbooks.[42,43,44,45,46,47]

Figure 6. The Flow of Participants into an Analysis[iii]



It is important to emphasize that cost-effectiveness analyses, much like safety and clinical effectiveness analyses, require collection of specific data elements suited to the purpose. Although cost-effectiveness-type analyses are becoming more important and registries can play a key role in such analyses, registries

[iii] Tooth L, Ware R, Bain C. Quality of reporting of observational longitudinal research. Am J Epidemiol 2005; 161(3):280–8. Reprinted with permission. Copyright restrictions apply.

traditionally have not collected much information on quality of life or resource use that can be linked to cost data.[48] To be used for cost-effectiveness analysis, registries must be developed with that purpose in mind.

5.1. Developing a Statistical Analysis Plan

5.1.1. Need for a Statistical Analysis Plan

It is important to develop a statistical analysis plan (SAP) that describes the analytical principles and statistical techniques to be employed in order to address the primary and secondary objectives, as specified in the study protocol or plan. Generally, the SAP for a registry study that is intended to support decisionmaking, such as a safety registry, is likely to be more detailed than the SAP for a descriptive study or health economics study. A registry may require a primary "master SAP," as well as subsequent, supplemental SAPs. Supplemental SAPs might be triggered by new research questions emerging after the initial master SAP was developed or because the registry evolved over time (e.g., additional data collected, data elements revised). Although the evolving nature of data collection practices in some registries poses challenges for data analysis and interpretation, it is important to keep in mind that the ability to answer questions emerging during the course of the study is one of the advantages (and challenges) of a registry. In the specific case of long-term rare-disease registries, many of the relevant research questions of interest cannot be defined a priori but arise over time as disease knowledge and treatment experience accrue. Supplemental SAPs can be developed only when enough data become available to analyze a particular research question. At times, the method of statistical analysis may have to be modified to accommodate the amount and quality of data available. To the extent that the research question and SAP are formulated *before* the data analyses are conducted and results are used to answer specific questions or hypotheses, such supplemental analysis retains much of the intent of prespecification rather than being wide-ranging exploratory analyses (sometimes referred to as "fishing expeditions"). The key to success is to provide sufficient details in the SAP that, together with the study protocol and the case report forms, describe the overall process of the data analysis and reporting.

5.1.2. Preliminary Descriptive Analysis to Assist SAP Development

During SAP development, one particular aspect of a registry that is somewhat different from a randomized controlled study is the necessity to understand the "shape" of the data collected in the study by conducting a simple stratified analysis.[15] This may be crucial for a number of reasons.

Given the broad inclusion criteria that most registries tend to propose, there might be a wide distribution of patients, treatment, and/or outcome characteristics. The distribution of age, for example, may help to determine if more detailed analyses should be conducted in the "oldest old" age group (80 years and over) to help understand health outcomes in this subgroup that might be different from those of their younger counterparts.

Unless a registry is designed to limit data collection to a fixed number of regimens, the study population may experience many "regimens," considering the combination of various dose levels, drug names, frequency and timing of medication use (e.g., acute, chronic, intermittent), and sequencing of therapies. The scope and complexity of these variations constitute one of the most challenging aspects of analyzing a registry, since treatment is given at each individual physician's discretion. Grouping of treatment into regimens for analysis should be done carefully, guided by clinical experts in that therapeutic area. The full picture of treatment patterns may become clear only after a sizable number of patients have been enrolled.

Consequently, the treatment definition in an SAP may be refined during the course of a study. Furthermore, there may be occasions where a particular therapeutic regimen is used in a much smaller number of patients than anticipated, so that specific study objectives focusing on this group of patients might become unfeasible. Also, the registry might have enrolled many patients who would normally be excluded from a clinical trial because of significant contraindications related to comorbidity or concomitant medication use. In this case, the SAP may need to define how these patients will be analyzed (either as a separate group or as part of the overall study population) and how these different approaches might affect the interpretation of the study results.

There is a need to evaluate the presence of potential sources of bias and, to the extent feasible, use appropriate statistical measures to address such biases. For example, the bias known as *confounding by indication*[49] results from the fact that physicians do not prescribe medicine at random: the reason a patient is put on a particular regimen is often associated with their underlying disease severity and may, in turn, affect treatment outcome. (See Chapter 18 for more detailed discussion and examples.) To detect such a bias, the distribution of various prognostic factors at baseline is compared for patients who receive a treatment of interest and those who do not. A related concept is *channeling bias*, in which drugs with similar therapeutic indications are prescribed to groups of patients who may differ with regard to factors influencing prognosis.[50] To detect such a bias, registry developers and users must document the characteristics of the treated and untreated participants and either demonstrate their comparability or use statistical techniques to adjust for differences where possible. (Additional information about biases often found in registries is detailed in Chapter 3.10.) In addition to such biases, analyses need to account for factors that are interrelated, also known as *effect modifiers*.[15] The presence of effect modification may also be identified after the data are collected. All of these issues should be taken into account in an SAP, based on understanding of the patient population in the registry.

5.2. Timing of Analyses during the Study

Unlike a typical clinical trial, registries, especially those that take several years to complete, may conduct intermediate analyses before all patients have been enrolled and/or all data collection has been completed. Such midcourse analyses may be undertaken for several reasons. First, many of these registries focus on serious safety outcomes. For such safety studies, it is important for all parties involved to actively monitor the frequency of such events at regular predefined intervals so that further risk assessment or risk management can be considered. The timing of such analyses may be influenced by regulatory requirements. Second, it may be of interest to examine treatment practices or health outcomes during the study to capture any emerging trends. Finally, it may also be important to provide intermediate or periodic analysis to document progress, often as a requirement for continued funding.

While it is useful to conduct such periodic analysis, careful planning should be given to the process and timing. The first questions are whether a sufficient number of patients have been enrolled and whether a sufficient number of events have occurred. Both can be estimated based on the speed of enrollment and rate of patient retention, as well as the expected incidence rate of the event of interest. The second issue is whether sufficient time has elapsed after the initial treatment with a product so that it is biologically plausible for events to have occurred. (For example, some events can be observed after a relatively short duration, such as site reactions to injections, compared with cancers, which may have a long induction or latency.) If there are too few patients or insufficient time has elapsed, premature analyses may lead to the inappropriate conclusion that there is no occurrence of a particular event. Similarly, uncommon events,

occurring by random chance in a limited sample, may be incorrectly construed as a safety signal. However, it is inappropriate to delay analysis so long that an opportunity might be missed to observe emerging safety outcomes. Investigators should use sound clinical and epidemiological judgment when planning an intermediate analysis and, whenever possible, use data from previous studies to help to determine the feasibility and utility of such an analysis.

When planning the timing of the analysis, it may be helpful to consider substudies if emerging questions require data that were not initially collected. Substudies often involve data collection based on biological specimens or specific laboratory procedures. They may, for example, take the form of nested case-control studies. In other situations, a research question may be applicable only to a subset of patients, such as those who become pregnant while in the study. It may also be desirable to conduct substudies among patients in a selected site or patient group to confirm the validity of study measurement. In such instances, a supplemental SAP may be a useful tool to describe the statistical principles and methods.

5.3. Factors to Be Considered in the Analysis

Registry results are most interpretable when they are specific to well-defined endpoints or outcomes in a specific patient population with a specific treatment status. Registry analyses may be more meaningful if variations of study results across patient groups, treatment methods, or subgroups of endpoints are reported. In other words, analysis of a registry should explicitly provide the following information:

- *Patient*: What are the characteristics of the patient population in terms of demographics, such as age, gender, race/ethnicity, insurance status, and clinical and treatment characteristics (e.g., past history of significant medical conditions, disease status at baseline, and prior treatment history)?
- *Exposure (or treatment)*: Exposure could be therapeutic treatment such as medication or surgery; a diagnostic or screening tool; behavioral factors such as alcohol, smoking habits, and diet; or other factors such as genetic predisposition or environmental factors. What are the distributions of the exposure in the population? Is the study objective specific to any one form of treatment? Is a new user design being used?[51] Does the exposure definition (index and reference group) and analysis avoid immortal-time bias?[52] Are there repeated measures or is the exposure intermittent?
- *Endpoints (or outcomes)*: Outcomes of interest may encompass effectiveness or comparative effectiveness, the benefits of a health care intervention under real-world circumstances,[53] and safety—the risks or harms that may be associated with an intervention. Examples of effectiveness outcomes include survival, disease recurrence, symptom severity, quality of life, and cost-effectiveness. Safety outcomes may include infection, sensitivity reactions, cancer, organ rejection, and mortality. Endpoints must be precisely defined at the data collection and analysis stages. Are the study data on all-cause mortality or cause-specific mortality? Is information available on pathogen-specific infection (e.g., bacterial vs. viral)? (See Case Example 24.) Are there competing risks?[54]
- *Covariates:* As with all observational studies, comparative effectiveness research requires careful consideration, collection, and analysis of important confounding and effect modifying variables. For medication exposures, are dose, duration, and calendar time under consideration? Directed acyclic graphs (DAGs) can be useful tools to illustrate how the exposure (or treatment), outcome and covariates are related.[55,56]
- *Time*: For valid analysis of risk or benefit that occurs over a period of time following therapy, detailed accounting for time factors is required. For exposures, dates of starting and stopping a treatment or switching therapies should be recorded. For outcomes, the dates when followup visits occur and whether or not they lead to a diagnosis of an outcome of interest, are required in order to take into account how long and how frequently patients were followed. Dates of

diagnosis of outcomes of interest or dates when patients complete a screening tool or survey should be recorded. At the analysis stage, results must also be described in a time-appropriate fashion. For example, is an observed risk consistent over time (in relation to initiation of treatment) in a long-term study? If not, what time-related risk measures should be reported in addition to or instead of cumulative risk? When exposure status changes frequently, what is the method of capturing the population at risk? Many observational studies of intermittent exposures (e.g., use of nonsteroidal antiinflammatory drugs or pain medications) use time windows of analysis, looking at events following first use of a drug after a prescribed interval (e.g., 2 weeks) without drug use. Different analytic approaches may be required to address issues of patients enrolling in a registry at different times and/or having different lengths of observation during the study period.

- *Potential for bias*: Successful analysis of observational studies also depends to a large extent on the ability to measure and analytically address the potential for bias. Refer to Chapter 3.10 for a description of potential sources of bias. DAGs can also be useful for understanding and identifying the source of bias.[55,56] Details and examples of quantification of bias can be found in Chapter 18. For detail on how to quantify potential bias, please see the textbook by Lash, Fox, and Fink.[13]

5.3.1. Choice of Comparator

An example of a troublesome source of bias is the choice of comparator. When participants in a cohort are classified into two or more groups of individuals according to certain study characteristics (such as treatment status, with the "standard of care" group as the comparator), the registry is said to have an *internal* or *concurrent* comparator. The advantage of an internal comparator design is that patients are likely to be more similar to each other (in contrast to comparisons between registry subjects and external groups of subjects) except for their treatment status. When defining the comparator group, it is important not to introduce immortal time bias.[52] In addition, consistency in measurement of specific variables and data collection methods may also make the comparison more valid. Internal comparators are particularly useful for treatment practices that change over time. Comparative effectiveness studies may often necessitate use of an internal comparator in order to maximize the comparability of patients receiving different treatments within a given study, and to ensure that variables required for multivariable analysis are available and measured in an equivalent manner for all patients to be analyzed.

Unfortunately, it is not always possible to have or sustain a valid internal comparator. For example, there may be significant medical differences between patients who receive a particularly effective therapy and those who do not (e.g., underlying disease severity or contraindications), or it may not be feasible to maintain a long-term cohort of patients who are not treated with such a medication. It is known that external information about treatment practices (such as scientific publications or presentations) can result in physicians changing their practice, such that they no longer prescribe the previously-accepted standard of care. There may be a systematic difference between physicians who are early adopters and those who start using the drug or device after its effectiveness has been more widely accepted. Early adopters may also share other practices that differentiate them from their later adopting colleagues.5

In the absence of a good internal comparator, one may have to leverage external comparators to provide critical context to help interpret data revealed by a registry. An external or historical comparison may involve another study or another database that has disease or treatment characteristics similar to those of registry subjects. Such data may be viewed as a context for anticipating the rate of an event. One widely-used comparator is the U.S. SEER cancer registry data, because SEER provides detailed annual incidence

rates of cancer stratified by cancer site, age group, gender, and tumor staging at diagnosis. SEER represents 28% of the United States population.[57] A procedure for formalizing comparisons with external data is known as *standardized incidence rate* or *ratio*;[15] when used appropriately, it can be interpreted as a proxy measure of risk or relative risk.

Use of an external comparator, however, may present significant challenges. For example, SEER and a given registry population may differ from each other for a number of reasons. The SEER data cover the general population and have no exclusion criteria pertaining to history of smoking or cancer screening, for example. On the other hand, a given registry may consist of patients who have an inherently different risk of cancer than the general population, resulting from the registry having excluded smokers and others known to be at high risk of developing a particular cancer. This registry would be expected to have a lower overall incidence rate of cancer, which, if SEER incidence rates are used as a comparator, may complicate or confound assessments of the impact of treatment on cancer incidence in the registry.

Regardless of the choice of comparator, similarity between the groups under comparison should not be assumed without careful examination of the study patients. Different comparator groups may result in very different inferences for safety and effectiveness evaluations; therefore, analysis of registry findings using different comparator groups may be used in sensitivity analyses or bias analyses to determine the robustness of a registry's findings. Sensitivity analysis refers to a procedure used to determine how robust the study result is to alterations of various parameters. If a small parameter alteration leads to a relatively large change in the results, the results are said to be sensitive to that parameter. Sensitivity and bias analyses may be used to determine how the final study results might change when taking into account those lost to followup. A simple hypothetical example is presented in Table 17.

Table 17. Hypothetical Simple Sensitivity Analysis

Impact of loss to followup on incidence rates per 1,000 in a study of 1,000 patients in a registry		
Various assumptions of the observed incidence rate	**Assuming a 10 percent loss to followup**	**Assuming a 30 percent loss to followup**
Assuming the incidence of patients lost to followup is X times the rate of incidence estimated in those who stayed in the registry:		
X=0.5	106	94
X=1	111	110
X=2	122	143
X=3	156	242

Table 17 illustrates the extent of change in the incidence rate of a hypothetical outcome assuming varying degrees of loss to followup, and differences in incidence between those for whom there is information and those for whom there is no information due to loss to followup. In the first example, where 10 percent of the patients are lost to followup, the estimated incidence rate of 111/1,000 people is reasonably stable; it does not change too much when the (unknown) incidence in those lost to followup changes from 0.5 times the observed to 5 times the observed, with the corresponding incidence rate that would have been observed ranging from 106 to 156 per 1,000. On the other hand, when the loss to followup increases to 30 percent, the corresponding incidence rates that would have been observed range from 94 to 242. This

procedure could be extended to a study in which there is more than one cohort of patients, with one being exposed and the other being nonexposed. In that case, the impact of loss to followup on the relative risk could be estimated by using sensitivity analysis. More examples are included in Chapter 18.

5.3.2. Patient Censoring

At the time of a registry analysis, events may not have occurred for all patients. For these patients, the data are said to be *censored*, indicating that the observation period of the registry was stopped before all events occurred (e.g., mortality). In these situations, it is unclear when the event will occur, if at all. In addition, a registry may enroll patients until a set stop date, and patients entered into the registry earlier will have a greater probability of having an event than those entered more recently because of the longer followup. An important assumption, and one that needs to be assessed in a registry, is how patient prognosis varies with the time of entrance into the registry. This may be a particularly problematic issue in registries that assess innovative (and changing) therapies. Patients and outcomes initially observed in the registry may differ from patients and outcomes observed later in the registry timeframe either because of true differences in treatment options available at different points in time, or because of the shorter followup for people who entered later. Patients with censored data, however, contribute important information to the registry analysis. When possible, analyses should be planned so as to include all subjects, including those censored before the end of the followup period or the occurrence of an event. One method of analyzing censored data to estimate the conditional probability of the event occurring is to use the Kaplan-Meier method.[58] In this method, for each time period, the probability is calculated that those who have not experienced an event before the beginning of the period will still not have experienced it by the end of the period. The probability of an event occurring at any given time is then calculated from the product of the conditional probabilities of each time interval.

For information about right censoring and left truncation, please see Chapter 18.

6. Summary of Analytic Considerations

In summary, a meaningful analysis requires careful consideration of study design features and the nature of the data collected. Most typical epidemiologic study analytical methods can be applied, and there is no one-size-fits-all approach. Efforts should be made to carefully evaluate the presence of biases and to control for identified potential biases during data analysis. This requires close collaboration among clinicians, epidemiologists, statisticians, study coordinators, and others involved in the design, conduct, and interpretation of the registry.

A number of biostatistics and epidemiology textbooks cover in depth the issues raised in this section and the appropriate analytic approaches for addressing them—for example, "time-to-event" or survival analyses[59] and issues of recurrent outcomes and repeated measures, with or without missing data,[60] in longitudinal cohort studies. Other texts address a range of regression and nonregression approaches to analysis of case-control and cohort study designs[61] that may be applied to registries.

7. Interpretation of Registry Data

Interpretation of registry data is needed so that the lessons from the registry can be applied to the target population and used to change future health care and improve patient outcomes. Proper interpretation of registry data allows users to understand the precision of the observed risk or incidence estimates, to evaluate the hypotheses tested in the current registry, and often also to generate new hypotheses to be

examined in future registries or randomized controlled trials. If the purpose of the registry is explicit, the actual population studied is reasonably representative of the target population, the data quality monitored, and the analyses performed so as to reduce potential biases, then the interpretation of the registry data should allow a realistic picture of the quality of medical care, the natural history of the disease studied, or the safety, effectiveness, or value of a clinical evaluation. Each of these topics needs to be discussed in the interpretation of the registry data, and potential shortcomings should be explored. Assumptions or biases that could have influenced the outcomes of the analyses should be highlighted and separated from those that do not affect the interpretation of the registry results. The use of a comparator that is of the highest reasonably possible quality is integral to the proper interpretation of the analysis.

Interpretation of registry results may also be aided by comparisons with external information. Examples include rates, or prevalence, of the outcomes of interest in other studies and different data sources (taking into account reasons they may be similar or different). Such comparisons can put the findings of registry analyses in the context of previous study results and other pertinent clinical and biological considerations as to the validity and generalizability of the results.

Once analyzed, registries provide important feedback to several groups, including the registry's developers. Analysis and interpretation of the registry will demonstrate strengths and limitations of the original registry design and will allow the developers to make needed design changes for future versions of the registry. Another group consists of the study's sponsors and related oversight/governance groups, such as the scientific committee and data monitoring committee. (Refer to Chapter 2.6 for more information on registry governance and oversight.) Interpretation of the analyses allows the oversight committees to offer recommendations concerning continued use and/or adaptation of the registry and to evaluate patient safety. The final group consists of the end users of the registry output, such as patients or other health care consumers, health services researchers, health care providers, and policymakers. These are the people for whom the data were collected and who may use the results to choose a treatment or intervention, to determine the need for additional research programs to change clinical practice, to develop clinical practice guidelines, or to determine policy. All three user groups work toward the ultimate goal of each registry—improving patient outcomes.

References for Chapter 13

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Case Examples for Chapter 13

Case Example 23. Using Registry Data to Evaluate Outcomes by Practice

Description	The Epidemiologic Study of Cystic Fibrosis (ESCF) Registry was a multicenter, encounter-based, observational, postmarketing study designed to monitor product safety, define clinical practice patterns, explore risks for pulmonary function decline, and facilitate quality improvement for cystic fibrosis (CF) patients. The registry collected comprehensive data on pulmonary function, microbiology, growth, pulmonary exacerbations, CF-associated medical conditions, and chronic and acute treatments for children and adult CF patients at each visit to the clinical site.
Sponsor	Genentech, Inc.
Year Started	1993
Year Ended	Patient enrollment completed in 2005; followup complete
No. of Sites	215 sites over the life of the registry
No. of Patients	32,414 patients and 832,705 encounters recorded

Challenge

Although guidelines for managing cystic fibrosis patients have been widely available for many years, little is known about variations in practice patterns among care sites and their associated outcomes. To determine whether differences in lung health existed between groups of patients attending different CF care sites and to determine whether these differences were associated with differences in monitoring and intervention, data on a large number of CF patients from a wide variety of CF sites were necessary.

As a large, observational, prospective registry, ESCF collected data on a large number of patients from a range of participating sites. At the time of the outcomes study, the registry was estimated to have data on over 80 percent of CF patients in the United States, and it collected data from more than 90 percent of the sites accredited by the U.S. Cystic Fibrosis Foundation. Because the registry contained a representative population of CF patients, the registry database offered strong potential for analyzing the association between practice patterns and outcomes.

Proposed Solution

In designing the study, the team decided to compare CF sites using lung function (i.e., FEV1 [forced expiratory volume in 1 second] values), a common surrogate outcome for respiratory studies. Data from 18,411 patients followed in 194 care sites were reviewed, and 8,125 patients from 132 sites (minimum of 50 patients per site) were included. Only sites with at least 10 patients in a specified age group (ages 6–12, 13–17, and 18 or older) were included for evaluation of that age group. For each age group, sites were ranked in quartiles based on the median FEV1 value at each site. The frequency of patient monitoring and use of therapeutic interventions were compared between upper and lower quartile sites after stratification for disease severity.

Results

Substantial differences in lung health across different CF care sites were observed. Within-site rankings tended to be consistent across the three age groups. Patients who were cared for at higher ranking sites had more frequent monitoring of their clinical status, measurements of lung function, and cultures for respiratory pathogens. These patients also received more interventions, particularly intravenous antibiotics for pulmonary exacerbations. The study concluded that frequent monitoring and increased use of appropriate medications in the management of CF are associated with improved outcomes.

Key Point

Stratifying patients by quartile of lung function, age, and disease severity allowed comparison of practices among sites and revealed practice patterns that were associated with better clinical status. The large numbers of patients and sites allowed for sufficient information to create meaningful and informative stratification, and resulted in sufficient information within those strata to reveal meaningful differences in site practices.

For More Information

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Case Example 24. Using Registry Data to Study Patterns of Use and Outcomes

Description	The Palivizumab Outcomes Registry was designed to characterize the population of infants receiving prophylaxis for respiratory syncytial virus (RSV) disease, to describe the patterns and scope of the use of palivizumab, and to gather data on hospitalization outcomes.
Sponsor	MedImmune, LLC
Year Started	2000
Year Ended	2004
No. of Sites	256
No. of Patients	19,548 infants

Challenge

Respiratory syncytial virus is the leading cause of serious lower respiratory tract disease in infants and children and the leading cause of hospitalizations nationwide for infants under 1 year of age. Palivizumab was approved by the U.S. Food and Drug Administration (FDA) in 1998 and is indicated for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease. Two additional, large, retrospective surveys conducted after FDA approval studied the

effectiveness of palivizumab in infants, again showing that it reduces the rate of RSV hospitalizations. To capture postlicensure patient demographic outcome information, the manufacturer wanted to create a prospective study that identified infants receiving palivizumab to better understand the population receiving the prophylaxis for RSV disease and to study the patterns of use and hospitalization outcomes.

Proposed Solution

A multicenter registry study was created to collect data on infants receiving palivizumab injections. No control group was included. The registry was initiated during the 2000–01 RSV season. Over 4 consecutive years, 256 sites across the United States enrolled infants who had received palivizumab for RSV under their care, provided that the infant's parent or legally authorized representative gave informed consent for participation in the registry. Data were collected by the primary health care provider in the office or clinic setting. The registry was limited to data collection related to subjects' usual medical care. Infants were enrolled at the time of their first injection, and data were obtained on palivizumab injections, demographics, and risk factors, as well as on medical and family history.

Followup forms were used to collect data on subsequent palivizumab injections, including dates and doses, during the RSV season. Compliance with the prescribed injection schedule was determined by comparing the number of injections actually received with the number of expected doses, based on the month that the first injection was administered. Infants who received their first injection in November were expected to receive five injections, whereas infants receiving their first injection in February would be expected to receive only two doses through March. Data were also collected for all enrolled infants hospitalized for RSV and were directly reported to an onsite registry coordinator. Testing for RSV was performed locally, at the discretion of the health care provider. Adverse events were not collected and analyzed separately for purposes of this registry. Palivizumab is contraindicated in children who have had a previous significant hypersensitivity reaction to palivizumab. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to palivizumab. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to palivizumab. Adverse reactions occurring greater than or equal to 10% and at least 1% more frequently than placebo are fever and rash. In post-marketing reports, cases of severe thrombocytopenia (platelet count <50,000/microliter) and injection site reactions have been reported.

Results

From September 2000 through May 2004, the registry collected data on 19,548 infants. The analysis presented injection rates and hospitalization rates for all infants by month of injection and by site of first dose (pediatrician's office or hospital). The observed number of injections per infant was compared with the expected number of doses based on the month the first injection was given. Over 4 years of data collection, less than 2 percent (1.3 percent) of enrolled infants were hospitalized for RSV. This analysis confirmed a low hospitalization rate for infants receiving palivizumab prophylaxis for RSV in a large nationwide cohort of infants from a geographically diverse group of practices and clinics. The registry data also showed that the use of palivizumab was mostly consistent with the 2003 guidelines of the American Academy of Pediatrics for use of palivizumab for prevention of RSV infections. As the registry was conducted prospectively, nearly complete demographic information and approximately 99 percent

of followup information was captured on all enrolled infants, an improvement compared to previously completed retrospective studies.

Key Point

A simple stratified analysis was used to describe the characteristics of infants receiving injections to help prevent severe RSV disease. Infants in the registry had a low hospitalization rate, and these data support the effectiveness of this treatment outside of a controlled clinical study. Risk factors for RSV hospitalizations were described and quantified by presenting the number of infants with RSV hospitalization as a percentage of all enrolled infants who were hospitalized. These data supported an analysis of postlicensure effectiveness of RSV prophylaxis, in addition to describing the patient population and usage patterns.

For More Information

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Chapter 14. Modifying and Stopping Registries

1. Introduction

Most, if not all registries, should undergo periodic critical evaluation by key stakeholders to ensure that the objectives are being met. When registry objectives are no longer being met or when clinical or other changes affect the registry (e.g., changes in treatment practices, the introduction of a new therapy), the registry may need to be adapted, or the registry may stop collecting new data. This chapter is divided into two sections. The first section describes possible reasons for a registry transition and issues that should be considered in planning and implementing a transition. The second section discusses factors that may lead to the determination to stop a patient registry. Case Examples 25, 26, 27, and 28 describe a variety of registry transitions.

2. Registry Transitions

A wide variety of factors may drive the decision to proceed with a registry transition. For example, a registry may need to transition to a new technology platform to remain functional for its participants, or a registry that was designed to study the natural history of a disease for which there was no effective treatment may change its purpose when a new product or therapy becomes available in the market. Other scenarios in which a transition may be necessary include changes in funding sources and stakeholders (e.g., funding for a government-sponsored registry may end resulting in transition to private ownership, such as to a professional association) or the introduction of new regulatory requirements (e.g., adapting a registry to fulfill a post-marketing commitment). Because many different factors may contribute to a registry transition, transitions are highly variable in scope and resource requirements.

This section focuses on issues that are of particular significance in a major registry transition, defined as a change in the 1) purpose, 2) sponsor, and/or 3) technology platform, all of which will have a substantive impact on the ongoing conduct of the registry. Less ambitious transitions (e.g., changes in data elements on preexisting case report forms) are not specifically covered herein; however, parts of this section (e.g., data analysis) are pertinent to such transitions.

While the considerations for a major registry transition are similar to those for the launch of a new registry, there are several distinguishing features. First, a registry transition is facilitated by an existing registry and the collective experience of conducting that registry. The existing registry can essentially serve as the starting point for creating a prototype of the revision. The planning and design of the registry transition should also benefit from lessons learned in operating the existing version of the registry. What has worked well and what has been problematic? What challenges have been encountered at every level, from staff entering data at the participating sites to the analyst creating reports? Indeed, one or more of these issues may be contributing factors in the decision to proceed with the registry transition. Even if this is not the case, the transition provides an opportunity to address these issues. Registry transitions also present unique challenges that are distinct from the development of a new registry. In particular, transferring data collected in an existing registry to the revised registry (i.e., data migration) can be a complex and resource-intensive process. (See Case Example 26.)

Despite these differences, the steps in the execution of a major registry transition are analogous to those involved in the launch of a new registry. Therefore, the section is organized in accordance with the

general framework for developing a new registry, with a planning and design phase, an implementation phase to carry out the project plan, and an assessment of the potential impact on data management and analysis.

2.1. Planning and Design

The planning and design of a registry transition begins with an assessment phase, in which the need for a transition is considered. Articulating the purpose(s), determining if a major registry transition is an appropriate means of achieving the purpose(s), and assessing the feasibility of a registry transition are important considerations, as such projects require a significant commitment of resources and have associated risks. Chapter 2.2.2. describes the assessment phase for a new registry, much of which is directly relevant to the consideration of a major registry transition. If the assessment leads to a decision to move forward, then the planning and design of the transition can proceed with the formation of a transition team and development of a comprehensive project plan that encompasses governance, ethical and legal issues, and technology considerations.

2.1.1. Forming a Transition Team

The creation of a project charter is often a useful starting point in assembling and focusing a transition team. A project charter typically includes the following information:

- Overview of the transition
- Purpose/justification for the transition
- Goals and objectives of the transition
- Business case for the transition (if applicable)
- Identification of major stakeholders
- Assumptions and constraints (organizational, environmental, and external)
- Potential risks
- Milestones/deliverables or high-level timeline
- Budget
- Transition team members
- References to source documents, if applicable (e.g., new clinical practice guidelines)

The next step is to assemble the transition team, which will be responsible for planning and implementing the registry transition. It is important to include key stakeholders and to think broadly about the talent and expertise needed to accomplish a successful transition. In general, the transition team should include the following members:

- Sponsor/funding organization representative: ensures that the team has the resources necessary to complete the project and keeps the sponsor apprised of any issues that may affect the timeline or budget for the transition.
- Project manager: accountable for all aspects of the transition, including timely escalation of issues for resolution.
- Clinical expert: provides guidance on changes that affect the clinical content of the registry (e.g., changes in purpose and data collection) and provides input on data migration, as needed.
- Epidemiologist/biostatistician: provides guidance on changes that affect the study design and analysis plans (e.g., changes in purpose, data collection, data management, and data migration).

- Data management expert: provides guidance on changes that affect data collection, data storage, or data quality assurance.
- Legal/ethical expert: provides guidance on how changes affect the legal and ethical construct of the registry (e.g., contract with funding source(s), contracts with participating sites, contracts with vendors, and data sharing agreements) and identifies any ethical issues (e.g., need for institutional review board review, changes to informed consent documents, need to re-consent participants).
- Other representatives: depending on the nature of the transition, other representatives may be included on the transition team such as 1) a principal investigator or study coordinator from a participating site with experience entering data into the registry to provide guidance on feasibility and burden of data entry, 2) a technical expert to help guide a transition to a new technology platform, 3) a patient advocate to gain the patient perspective, and/or 4) representatives of other databases that are linked to the registry (e.g., a related registry or substudy).

Once the transition team has been assembled, it is critical to achieve consensus on the rationale and the overarching goal(s) for the registry transition. Open discussion at this stage may identify unanticipated barriers, which can be addressed proactively in the transition planning. Gaining the full support of the transition team will increase the likelihood of a successful registry transition.

2.1.2. Developing a Project Plan

The next step for the transition team is to develop a detailed project plan encompassing timeline and budget. The transition project plan should be thoughtful, complete, and realistic. As with all projects of this magnitude and complexity, disagreement among stakeholders over scope, cost overruns, and time delays may occur. These predictable issues should be anticipated, as much as possible, and risk mitigation strategies considered. The project plan should also consider other sources of risk specific to the transition (e.g., unexpected issues with technology compatibility, delays in obtaining institutional review board approval, and disputes related to ownership issues). Chapter 2 provides more information on project planning considerations.

The project plan should also address staffing issues. The transition may require new expertise and skills that alter staffing requirements. Training existing employees or hiring appropriately skilled personnel may be necessary. Planning for additional workload on the registry staff during the actual transition is also an important consideration, as they may be operating and supporting the existing registry while working on the transition to the modified registry.

Other issues that should be considered in transition planning relate to governance, ethical concerns, legal matters, data collection, and technology. These issues are discussed in more detail in the following sections.

2.1.3. Governance Issues

Nearly all registry transitions will require an internal and external governance structure to manage and approve changes, whether the transition relates to the scientific objectives of the registry, technology changes, or data access. The transition team is one important component of the governance structure. Chapter 2.6 reviews the governance considerations for the planning of a new registry, many of which are relevant to a registry transition. Some additional considerations are addressed below.

2.1.3.1. Scientific Advisory Board Governance during the Transition

Many registries have scientific advisory boards that oversee the conduct of the registry. These boards may also play a role in governance during a registry transition and provide external perspective for the considerations and future objectives for a registry transition. Membership of the scientific advisory board should be reviewed to ensure the key stakeholders that are involved in the transition are represented. During the registry transition, the scientific advisory board can also act as an advocate of change by publicly supporting the transition and helping to engage and motivate clinicians at the participating centers. External stakeholders, such as patient advocacy groups and regulatory agencies/health authorities, may also be informed of the transition and, depending on the goals of the transition, potentially enlisted as additional public advocates for the registry transition.

2.1.3.2. Governance of Data Access

Registry transitions will also require revisiting the data access policies and procedures. If a data access committee is already in place, the committee should be charged with 1) determining how changes in the registry will affect the policies and procedures for accessing data, and 2) reviewing the operational plan for executing analysis plans with respect to the registry transition. Furthermore, if the transition involves a change in registry stakeholders, the procedures for conducting analyses and developing publications should be re-examined. New stakeholders may need to be involved in the prioritization of analysis plans, conduct of analyses, and/or the review of scientific abstracts and manuscripts.

2.1.4. Ethical and Legal Issues

The major ethical and legal issues for registries focus on data privacy, patient confidentiality, and ownership of and access to the data. These issues, covered comprehensively in Chapter 7, should also be carefully considered during a registry transition. It is important to note that interpretations of the pertinent laws and regulations are numerous and varied, leading to inconsistent application among institutions, which may affect multicenter registries.[1] Hence, input from legal counsel and regulatory authorities should be sought when planning a registry transition. Some common legal or ethical concerns that may arise during registry transitions are reviewed below.

An early step in the registry transition planning process is consideration of the need for institutional review board (IRB)/ethics committee (EC) review. If the purpose of the registry is unchanged and no new data are being collected, IRB/EC review may not be necessary – subject to ethical guidelines and the requirements of the individual IRBs/ECs. However, IRB/EC review would likely be required in certain transitions, such as if new data will be collected through contact with patients, if the new data that will be collected includes identifiable personal information, or if the data will be used in a different manner than previously communicated to patients (45 CFR §46.102(f)).

A registry transition may involve extending the followup period of the initial cohort. In these circumstances, re-contacting patients or using their identifiers may be necessary to collect the longer-term data. This may require modification of informed consent documents and amended protocols. For example, a cardiac assist device registry may have been established initially to determine perioperative safety. However, new safety concerns associated with longer-term implantation may prompt a change in the purpose of the registry. Medical records, death indices, and patient interviews may be required to collect the longer-term followup data. This new data collection effort would likely require IRB/EC review.

Consideration should also be given to whether any changes will be required in the informed consent process (e.g., obtaining revised consents from existing subjects, obtaining new consents for registries that do not currently have such consents). If consent was obtained for registry participation initially, re-consenting may be needed, especially when the registry transition will result in (1) longer or otherwise different followup than what was originally agreed to by patients, (2) direct contact with patients to obtain new data, (3) collection of biological samples or linkage of existing specimens to registry data, (4) the use of data from deceased participants, or (5) linkage of the participant's data to other databases. If the planned registry modifications involve patients for whom the feasibility of obtaining consent would require unreasonable burden or situations where the consenting process would potentially introduce an unacceptable level of bias,[2,3,4] discussions with local IRBs/ECs should be undertaken to see if the consent can be waived. Chapter 8 discusses these issues in more detail.

2.1.5. Data Collection

A major component of the registry transition project plan should be a thorough evaluation of current and future data collection needs. The project plan should allocate time for epidemiologists and clinical experts to jointly review the current registry case report form (CRF). It is of paramount importance that the relevance of the current set of data elements is reviewed, in light of what is known about new hypotheses to be tested. During this review, some data elements may deemed irrelevant and may not be required moving forward. When considering the collection of additional covariates and outcomes, particular attention must be given to balancing the scientific relevance of the new data elements with the logistical burden on participating centers.

Additional considerations may arise if a registry transition involves one of the following specific circumstances.

2.1.5.1. Collection of Biological Samples

Biobanks, defined as facilities that store biological material (e.g., serum, genomic material, pathology specimens) from humans, are increasingly popular additions to registries.[5] The addition of a biobank raises many logistical issues, which are outside the scope of this chapter. However, it should be noted that the addition of a biobank will likely require changes in the informed consent. Some biobanks have used general consents to cover future analyses of the biological material and integration into the registry, but there is significant concern about these broad consent documents. Some commentaries on this issue have suggested that such broad consents are more appropriate when limited to a specific disease entity, thereby allowing for studies examining diagnosis, mechanisms of disease, risk factors, and treatment outcomes.[6,7,8] Chapter 8 discusses these issues in more detail.

2.1.5.2. Pediatric Registries

If a registry enrolls pediatric participants and the registry transition involves extending the followup period, consideration should be given to whether participants need to be consented when they reach an eligible age. This is particularly important for those registries that plan to add a biobank or link to other databases as part of the transition process. There is considerable debate regarding the ethics of parents enrolling their children in research studies. More discussion on this topic can be found in Chapter 7. It is also important to note that for all registries, the right to withdraw is inherent;[8,9] see Chapter 8.

2.1.5.3. National to International Registry

Some registry transitions may extend the geographic scope of a registry. For example, a U.S.-based registry may add participating sites in Europe. When the registry scope extends beyond national borders, additional ethical and legal concerns must be addressed. Each country may have different legislation and restrictions for the collection and processing of subject information and its use for research. Adequate time and additional resources to investigate these requirements should be factored into the project plan. Moreover, if Federal funds are used in the registry transition, additional steps may be involved in the expansion of the registry. In particular, some registries may be collecting data on vulnerable international populations for which additional privacy protection safeguards may be necessary. Federal guidelines for performing international research should be consulted as part of the planning process.

2.1.6. Data Ownership and Licensing

A number of scenarios exist in which ownership of registry materials must be delineated, including the interface, platform, infrastructure, and data. During a registry transition, particularly one involving a change in stakeholders, a careful review of agreements or contracts should be performed to determine if modifications are needed. In some cases, the registry transition may involve moving data from one platform to another. Hence, data ownership may need to be clarified. For example, a professional organization may determine that the vendor maintaining its registry is performing below expectations and may select a new vendor to house and run the registry. Depending on the terms of the prior agreements, it may or may not be possible to import the historical data into the new vendor's system.

Registry data are often collected using electronic or paper CRFs that may have intellectual property protections, including copyright, trademark, and patent. Measures should be taken to ensure that the appropriate permissions for use are still applicable when the registry transitions if continued use of these forms is planned.

2.1.6.1. Data Access

In addition to data ownership, ongoing and future data access is an important consideration. The new and ongoing registry stakeholders should consider whether the previous stakeholders should have access to the previously collected data as well as to the data collected in the future. Federal and academic stakeholders may need to execute technology transfer agreements (e.g., material transfer agreements) or other contractual agreements in order to access the data.

2.1.6.2. Changes in Funding

Registry transitions may also include changes in funding. For example, a registry that was initially funded through a government grant may be transitioned to a professional association or industry partner. When funding sources change, the role of the funding entities should be clearly delineated to ensure that there is no real or perceived threat to privacy or data confidentiality.

In some cases, a change in funding may require contract modifications in anticipation of potential conflicts between the new stakeholders and the remaining stakeholders. For example, industry may elect to partially fund a registry that is also receiving Federal funding from a regulatory agency. Contracts may need to be modified to clearly delineate how each set of funds will be spent. The new chapter on public-private partnerships provides more information on these issues. As with all contracts involving Federal funds, attention should be given to regulations governing their appropriate use. Additionally, changes in funding may alter where legal rights and obligations vest. It is important to have unambiguous

conversations with stakeholders and associated contractual agreements that clearly delineate the rights of the funding entities.

When data are transferred from one owner/sponsor to another, the liability associated with the protection of subjects' information should be clarified. Consideration should be given to indemnification clauses in data transfer agreements. Oftentimes, the data transfer agreements detail that the new sponsor of the registry will accept all liability for use of the data previously collected by the transferring sponsor. The data transfer agreement should also contain a clause that the new sponsor agrees to use the data properly. In these circumstances, the liability would be assumed by the new sponsor if there was a breach of information whereby subject-level information is relayed to an outside party. If the new sponsor is a Federal entity, however, there are regulations that prohibit the Federal government from indemnifying others (e.g., Anti-Deficiency Act).

2.1.6.3. Contracts with Vendors

Issues may arise with vendors (including inadequate performance of duties, loss of financial solvency, or escalating cost of renewing the contract), necessitating a transition to a new vendor. In light of these potential outcomes, it is necessary to draft contracts that consider these scenarios and contain provisions to address them. For example, if a registry is being transitioned to a new, fledgling company, consideration should be given to establishing an escrow account for the registry. This account would cover the cost of ensuring that the data remain accessible to the sponsoring body. Moreover, it prevents the registry from being part of the estate if the company is unable to meet its contractual obligations. Establishing the escrow account would increase the cost of the initiative for the sponsor, the vendor, or both and should be considered when planning the transition. In addition, contracts should contain explicit clauses that guarantee the transmission of data to a new vendor when the contract expires or if the vendor defaults on the contract.

2.1.7. Technology Considerations

A registry designed to collect long-term followup data will inevitably undergo technology changes. Platforms for electronic data capture (EDC) may be upgraded (such as version updates within a system), or the registry sponsor may select a different third party vendor to host the EDC system. Upgrading the EDC system and technology platform may enable more frequent data entry from participating centers, rather than annual or semi-annual data reporting under previous technology environments. Such changes have implications on training plans for participating centers (see below). Technology considerations relevant to linkage of a registry to an electronic health (medical) records (EHR/EMR) or other database and for collection of patient reported outcomes are covered elsewhere in this volume.

In transitioning to a new registry technology platform, it is important to clearly define software requirements to avoid design flaws, which are costly to correct after project completion. Soliciting input from various stakeholders (e.g., data entry personnel, clinical experts, data analysts) may be helpful to validate the proposed design of the new registry. The proposed design should be presented to them in an easy-to-understand format (e.g., a prototype) rather than a detailed requirements document, which may be more difficult to comprehend. Setting aside time for user acceptance testing (OAT) or pilot testing may also be useful to identify issues before the transition is complete.

One of the earliest and most important decisions in transitioning to a new technology platform is whether to develop the platform in-house or to use an external vendor. Each approach has advantages and

disadvantages. The in-house approach requires personnel with the appropriate expertise and the infrastructure to support such a project. Development tools widely used by software companies should be employed, if possible, to mitigate the risk of experiencing shortages of qualified personnel for ongoing support and maintenance of the application. Organizations that do not have the internal resources and expertise to develop a registry application in-house usually turn to external vendors. Selecting a registry vendor is an important strategic decision for an organization, particularly for sponsors who anticipate operating the registry for many years. Some factors that should be considered in selecting a registry vendor are outlined in Table 18 below.

Table 18. Considerations in Selecting a Registry Vendor

• Develop detailed requirements for the new registry before issuing a request for proposals. The requirements may be modified later to align with the vendor's framework for development, but having complete requirements early in the process will allow for a more accurate timeline and cost estimate.
• Gather as much information as possible about the potential vendor by contacting existing clients and asking detailed questions about communication, timelines, budget, and post-release support.
• Ask an independent expert to evaluate and analyze the technology platforms and technology expertise of the potential vendor.
• Ask the potential vendor to be specific with their cost estimates. Avoid vendors that cannot provide concrete estimates.
• Know the hosting and maintenance fees of the existing registry and compare them to the hosting and maintenance estimates from the potential vendor.
• Assess the security policies and procedures established by the vendor and ensure that they comply with the industry standards and best-of-breed practices.
• Assess the ability and willingness of the potential vendor to transfer registry data (both transfer of historical data into their registry application and transfer out from their registry application if the registry changes vendors in the future).
• Learn about the vendor's experience in importing data from other sources of medical information using standard interfaces (e.g., HL7, CDISC) and also about their ability to build custom interfaces. A list of existing and emerging standards in the field is maintained by U.S. Food and Drug Administration (FDA).
• Consider the vendor's international experience, including translation and help desk support, if pertinent to the planned transition.
• Discuss policies related to data access, including how participating sites can access their own data and how the registry team can obtain datasets for analysis.

Once a vendor has been selected and the features of their technology platform are known, it is important to assess the hardware, software, and browser configurations at the participating sites, as these may affect performance of the registry application. It is also important to ensure that the participating sites have access to the optimal configurations on which the application has been tested and validated. Requesting a technology contact person at each of the participating sites may be helpful to facilitate working through these issues during the transition.

Another technology consideration is transitioning personnel involved in data entry at participating sites from an existing registry to the new registry. This requires an analysis of security levels in order to transfer users to the appropriate permission level in the revised registry. In some cases, users can be transferred electronically from the existing to the new registry application, but in other cases, they must be added manually. The transition team must develop a plan for accomplishing the transfer that minimizes

the effort at the participating sites, but ensures only valid users can access the registry at the appropriate permission level. Of note, a registry transition provides an opportunity to assess the activity level of users at the participating sites and their ongoing need to access the registry.

A final technology consideration pertinent to a transition relates to the closeout of an existing registry. Generally, the closeout should be scheduled well after the anticipated launch of the new registry, as timelines on such complex projects are often delayed. The existing registry may also be useful in validating successful data migration into the new registry.

2.2. Implementation

Once a transition plan has been developed and the decision has been made to move ahead, it is important to communicate with stakeholders about the plans, train registry participants on the changes and support them through the launch, and assess the impact of the transition on data management and analysis activities.

2.2.1. Communication

Communicating with all stakeholders is critical during a registry transition. The transition team should develop a communication plan that defines who is responsible for communicating what and to whom. The frequency and mode of communication should be established with a particular sensitivity to key stakeholders. Since the registry transition will likely disrupt workflow at the participating sites, communicating the rationale for the change, the timeline, and the impact on users is important. Any change in expectations or incentives for participation should be fully explained. It is important to anticipate and respond to questions and concerns from participating sites, knowing that change can lead to stress and anxiety. In most circumstances, the communication plan will focus on retaining participating sites through the transition. However, a registry transition provides an opportunity to evaluate participating centers to decide whether all of them should be retained. A transition may also be an ideal time to recruit additional sites.

2.2.2. Training

The development and implementation of a robust training program prior to the registry transition will facilitate the roll out of the revised registry and improve the quality of data collected. Training needs will vary according to the scope of the registry transition. For example, a technological change that affects the user interface, functionality, and/or organization of the data elements will likely require extensive training, whereas a transition related to a change in purpose with minimal impact on data entry should require less training. When developing a training program, the key elements of adult learning theory[10] should be kept in mind, and several questions should be addressed:

- Who is the intended audience? Determining the audience will have a significant impact on the design and implementation of the training program. For example, internal staff training will differ from that of external registry participants and the training program for clinicians will likely differ from that designed for data entry personnel.
- What are the learning objectives? The learning objectives should drive the development of the curriculum. What do the people involved in the registry need to know to be successful during and after the transition? The focus should be on what will change and why, and the impact of the changes on registry participants.

- What information is needed to meet the learning objectives? High-level overviews and detailed documents are useful to help participants with varying levels of interaction with the registry understand the changes. The creation of a reference guide that clearly describes what changes were made and why each change was made will be extremely helpful to some registry participants.
- What are the best mechanisms for disseminating the information? People respond differently to various learning environments and techniques. Depending on the size of the registry, training may be offered in various ways, some of which are described below:
    - Conference calls can be effective for smaller groups and allow for open discussion.
    - Webinars can be useful when larger groups are involved and the training activity includes visual presentation.
    - Face-to-face meetings are frequently effective since the learner is less likely to be distracted.
    - One-on-one training sessions are usually well received, since the training can be customized to the individual learner. However, this approach is costly.
    - User's guides, manuals, FAQs, and other documents can be posted on a website, or hard-copy materials can be distributed to participants.
- What is the best approach to ensure that learning has occurred? It is important to confirm that the training program is successful, in order to avoid issues with retention and data quality after the transition launch. Learning assessment approaches include tests (e.g., the completion of a sample data collection form or other task), surveys, and direct feedback. Feedback from the learning assessments should be incorporated into the training program, as needed. Pilot testing may also be useful for refining and strengthening the training program before launch.

2.2.3. Supporting Participants through the Registry Launch

In addition to a robust training program, sufficient personnel and resources should be assigned to respond to input and inquiries from registry participants following the launch of the revised registry. Accessibility of the support team is very important during this critical period of the transition. Planning for the registry launch should delineate how users can submit questions or concerns (e.g., by e-mail or calling a support desk), who will be the first responders, and how complex issues will be escalated for further evaluation. Many straightforward questions (e.g., problems logging on) can be resolved quickly and efficiently. However, it is important to carefully assess all input from participants since they may uncover problems with the revised registry that have been missed during testing. Such problems may require immediate attention not only from support personnel, but also from the developers of the registry application. At some defined point in time (e.g., 1 to 3 months after launch), a broader analysis of all of the questions and comments from participants may be helpful in prioritizing any further changes to the registry.

2.2.4. Data Management

Technological changes may require a change to the database/data warehouse used to store the registry data. Database or data warehouse transfers are complex processes that involve a number of steps, including creating a new database layout, mapping the legacy data to the new database layout, and transferring the data with rigorous quality controls to ensure that the transfer is successful. Database transfers also need to be conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and any regional IRB or EC approvals to ensure that the privacy of any patient-level data is maintained. The size and complexity of the registry as well as the extent of the

changes in the CRFs will determine the complexity of the data mapping process. The data fields known to users of the registry might be collected in different contexts (e.g., with added specificity or new dependencies between data elements on CRFs) and these differences must be considered in the data mapping process. Relatively small changes in the wording of a question on the CRF, or creating an additional category on an existing item (e.g., expanding categories of ethnicities) may introduce ambiguities in mapping the existing dataset to the new environment. In other instances, significant changes to the definition of an outcome variable will typically require review and adjudication of prior cases to establish longitudinal consistency across the dataset (for further detail, see Section 2.3.3. below). For these reasons, input and evaluation of the impact of the migration on future registry outcome analyses from subject matter experts, including epidemiologists and clinical experts, along with documentation of decision rules that were established during the epidemiological and clinical review, will be needed in the data mapping process. The effort and expense involved in the data migration is often underestimated and adequate time must be allocated during the project planning and in establishing timelines. Despite careful attention to detail, this activity often becomes an iterative process, with data mapping, data importation, and quality control checks that lead to corrections in the data mapping, re-importation of the data, etc.

Many practical issues should be considered when transferring a database. First, it is important to document the rationale for adding, modifying, or deleting data fields, so that this information can be communicated to stakeholders and registry participants. Second, carefully consider the future impact of changes. Certain changes may make it difficult to link prior datasets with the new datasets. For example, adopting a new, broader definition may mean that data can only be linked in one direction, as shown in Table 19.

Table 19. Impact of Definition Changes on Data Linkage

Old Definition	New Definition	Linkage Direction
Death: A mortality that occurred in the hospital within 30 days of the procedure.	Death: a mortality that occurred within 30 days of the procedure, whether in the hospital or not.	Deaths in the old dataset fall within the parameters of the new definition. However, deaths according to the new definition would not necessarily apply to the old definition since they include mortalities post-hospitalization.

When making changes to the data structure, the following questions should be considered:

- Will existing queries (i.e., questions raised by a data manager and issued back to the participating centers regarding a data entry issue) need to be rewritten for the new dataset?
- Will existing reports (e.g., percent of patients with a lab value above a certain number) need to be revised for the new dataset?
- Will more server space be needed to house the data?
- How can the impact of the changes on the processes affected by the new data structures be minimized?

It is also important to determine what metadata (e.g., long name, short name, data type/data format, and permissible values) are important to capture for each field and how the transition will affect the metadata.

2.3. Data Analysis

A registry transition may introduce many data analysis considerations that require the input of epidemiologists and/or biostatisticians. Transitions that involve new hypotheses or technological changes can present enormous challenges to the continuity and validity of the analyses. The issues range from the handling of new data elements to the introduction of selection bias or recall bias if the cohort definition evolves during the transition.

2.3.1. Changes in Cohort Definition

A registry transition may involve a change in the inclusion or exclusion criteria for patient participation, thus shifting the definition of the study cohort. These changes can occur under a number of scenarios, such as if the registry moves from a disease-based cohort (i.e., no inclusion criteria for receiving a particular treatment) to focusing on a cohort of patients with the disease who receive a specific therapy or class of therapies (i.e., inclusion criteria now requires patients to be receiving a treatment). Cohort definitions may also change based on geography (e.g., if a registry transitions from a national to a global catchment area). This introduces the possibility of geographic differences in disease severity or treatment patterns, which may require thorough documentation of baseline clinical status in order to stratify or perform covariate adjustment, if necessary.

Other changes in the cohort definition may occur if the registry transitions from having broad participation by centers to a limited set of centers (e.g., physicians who are associated with large specialty care clinics). A registry transition that results in such a change in the cohort definition has the potential to introduce selection bias into the registry by focusing the enrollment and ongoing followup of subjects on a potentially more severely affected group of patients. As enrollment and followup occur, epidemiologists should be actively involved to assess if selection bias has been introduced. Comparisons of demographic and baseline clinical features of subjects before and after the transition may be sufficient to assess the degree of bias introduced and to understand which factors or variables can be considered for stratification or covariate adjustment. Advanced methodologies such as comorbidity indices or propensity score analyses may be necessary to adequately adjust for the changes in the cohort over time.

2.3.2. Introducing New Data Elements

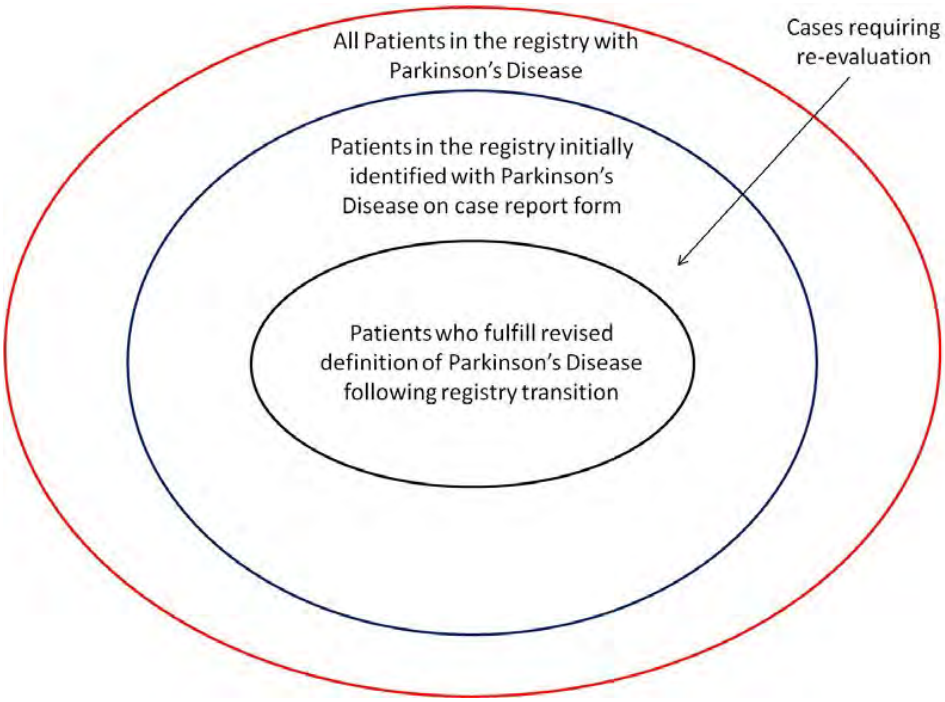
As scientific advances further the understanding of a particular disease or new treatments become available, new hypotheses will likely be formed. In order to test new hypotheses, adding data elements and/or refining the definition of existing data elements may be necessary. When adding new data elements, common data elements and validated instruments should be used, when possible (see Chapter 4). Validating new data elements, through source document verification of the original medical records, laboratory tests, or diagnostic reports, may be required. Results of source document verification may show there are discrepancies in the accuracy of new data elements being captured. For example, investigators interested in collecting data on heart failure as an outcome may find variation in how the definition of heart failure is applied across contributing centers. While the refinement of definitions for data elements occurs, analyses on the outcome variables may still take place. However, methods of quantitative sensitivity analysis may be necessary to understand the degree to which misclassification of variables may introduce bias into the analytic results. Results of source document verification efforts can be used as inputs into quantitative sensitivity analysis to directly estimate the sensitivity and specificity of the outcome variable.

2.3.3. Impact on Existing Cases of an Outcome

A registry transition may lead to redefining an outcome in order to increase sensitivity and specificity. For example, a registry that has been collecting data about the onset of Parkinson's disease as an outcome measure may transition to more stringent inclusion and exclusion criteria. Although this may result in increased validity of the outcome, the statistical power of the analyses from the registry may be compromised, as there will likely be fewer patients meeting the case definition going forward. Patients who have already been identified in the registry as cases may require re-evaluation (and possibly re-adjudication) to determine if their clinical scenario fulfills the revised selection criteria.

Figure 7 shows the potential impact of a change in an outcome (e.g., case definition of Parkinson's disease) following a registry transition. Note that the smaller cohort size following the registry transition may reduce statistical power and cases that met original case definition may require re-evaluation.

Figure 7. Potential Impact of a Change in Outcome



2.3.4. Impact of Patient Reported Outcomes

Registries frequently include patient reported outcomes, such as the SF-36® health survey or activities of daily living. It is important to note and characterize whether the type of patients and their disease severity or outcome status who are reporting self-assessments to the registry is changing over time because of the transition. If such instruments are introduced during a registry transition, patients may begin to preferentially recall events, which can lead to a bias in the outcomes. In addition, if the registry transitions from a purely disease-based registry to a therapy- or product-based registry, patients who become aware of this change may begin to report their health status more or less favorably.

Table 20 illustrates the possible consequences of transitioning from a disease-based registry to a focus on patients with the disease exposed to a particular therapy. Prior to the transition, the risk of the outcome

among exposed and unexposed patients was similar. Following the transition, there are more exposed patients, and, for the purposes of illustrating the impact of bias, assume awareness of the registry transition results in exposed patients preferentially reporting onset of a particular outcome. Because of this preferential report, the risk is approximately 25% greater among the exposed as compared to prior to the transition. The apparent risk ratio is now 1.46 comparing exposed to unexposed.

Table 20. Possible Consequences of a Change in Registry Focus

	Exposed	Unexposed
Before Transition		
Cases with specific patient- reported outcome	70	50
Total Patients	450	375
Cumulative Incidence per 100	15.6	13.3
Risk Ratio	1.17	
Following the Transition*		
Cases with specific patient- reported outcome	175	50
Total Patients	900	375
Cumulative Incidence per 100	19.4	13.3
Apparent Risk Ratio	1.46	

** The emphasis on enrolling patients who have been exposed to the therapy leads to an apparent 25% increase in the incidence of cases among the exposed.*

2.3.5. Comparative Effectiveness Analysis

A registry may transition from a disease-based cohort to one that is focused on specific treatment(s) in order to establish comparative effectiveness studies between multiple treatments. A greater emphasis on baseline covariate data may be required in this situation, and epidemiologists should be involved to identify the key variables that would account for differences in disease severity between the treatment groups in order to mitigate bias such as confounding by indication. Epidemiologists must also be involved in planning the statistical analysis, which may require matching techniques or other multivariate statistical techniques.

2.3.6. Biostatistics and Statistical Power

Statistical power must be considered in registry transitions that lead to changes in the size of the cohort and/or the extent of followup. For example, a transition that focuses the registry on a smaller number of participating centers may diminish the number of new enrollees, but have the benefit of providing an extended length of followup. The transition may eventually provide a greater number of exposed patients who develop the outcome(s) of interest. Biostatisticians should be involved in assessing the impact of changes in cohort accrual on statistical precision of the analyses. Previously specified hypotheses of interest may no longer be testable from the standpoint of statistical power. Alternatively, consideration of statistical power for newly specified hypotheses following the transition may provide an assessment for the extent of enrollment and followup required for robust future analyses.

2.4. Summary of Registry Transition Considerations

Many registries will undergo a major transition at some point in their lifecycle, most often related to a change in purpose, sponsor, and/or technology platform. A major registry transition is a complex and resource-intensive process with associated risks. Careful and comprehensive planning will maximize the probability of success. However, unexpected challenges may still occur during the implementation phase.

The transition team should be prepared to react to circumstances as they arise and modify the project plan accordingly. This chapter has reviewed the steps involved in the execution of a registry transition, including the planning and design, implementation, subsequent impact on data management and analysis issues. Table 21 presents a checklist of key issues that may be helpful to readers who are considering a major registry transition.

Table 21. Checklist of Key Considerations for a Registry Transition

Planning and Design Phase

1) **Determine if a registry transition is appropriate and feasible.**
    a. Has the purpose of the transition been clearly articulated?
    b. Is a transition an appropriate means of achieving the purpose?
    c. Is the transition feasible from a resource perspective?
2) **Organize a transition team.**
    a. Has a transition team been assembled with all necessary areas of expertise?
    b. Is the team in agreement on the rationale for and goals of the transition?
    c. **If applicable, how will partner organizations be involved in the transition planning and design?**
3) **Develop a transition project plan.**
    a. Does the project plan cover timeline, budget, and staffing?
    b. Have 'lessons learned' from operating the current registry been considered and addressed in the transition plan, as necessary?
    c. Have major risks been identified and risk mitigation strategies considered?
4) **Engage advisory boards and other stakeholders.**
    a. Is the scientific advisory board in agreement with the rationale for and goals of the transition?
    b. Are any changes to the scientific advisory board needed to ensure that appropriate areas of expertise for the transition are represented?
    c. Will changes to the data access policies and procedures be necessary?
5) **Consider legal and ethical issues.**
    a. Will the changes require review/approval by an IRB/EC?
    b. Do the changes require informed consent, or does the existing informed consent form need to be updated?
    c. Is the registry expanding to collect data in new countries? If so, what additional ethical and legal considerations must be addressed?
    d. Are any changes needed to existing contracts or agreements?
6) **Assess the potential impact of technology changes.**
    a. Does the transition involve changing to a new technology? If so, have the hardware, software, and browser configurations been assessed at participating sites to ensure that the new technology will perform well?
    b. Is there a plan for transferring personnel (usernames/passwords) from the previous system to the new system?
    c. Will a new registry vendor be selected? If so, have potential vendors been thoroughly assessed (see Figure 7)?

Implementation

1) **Share information on the transition with registry participants and stakeholders.**

a. Is there a communication plan that clearly defines who should communicate what information to whom and at what time?
b. Who will answer questions about the transition?

2) **Train registry participants and support them through the launch.**
   a. Have training plans been developed for registry staff and participants?
   b. Is there sufficient registry staff to carry out training for participants?
   c. Have registry materials (e.g., user guides, data definitions) been updated?
   d. Has a plan been developed to support participants after launch of the revised registry?

Data Management and Data Analysis

1) **Develop a plan for data migration.**
   a. Is data mapping or migration necessary?
   b. Are the timeline and budget sufficient for data migration, which is often an iterative, complex process?
   c. Is there a clear rationale for adding, modifying, or deleting each data field?
   d. Have the implications of changes to the data structure been carefully considered?
2) **Determine how the transition may affect data analyses.**
   a. Did the transition change the definition of the study cohort? If so, has the potential for selection bias or recall bias been assessed?
   b. Have new or modified data elements been reviewed to determine if participants are reporting this information correctly?
   c. Have outcome measures been redefined? Will existing cases of the outcome require re-adjudication?
   d. If comparative effectiveness research is planned, will additional baseline covariates be needed for the analyses?
   e. Will the transition affect the statistical precision of the analyses?

3. Planning for the End of a Patient Registry

Once a registry is in place, how long should it continue? What are reasonable decision criteria for stopping data collection? This section considers the issues related to stopping a patient registry study and suggests some guidelines. Although the specific answers to these questions will vary from study to study, the types of considerations may be more general. The discussion here is focused on registries intended to assess specific safety or effectiveness outcomes rather than those intended to assess health care operations, such as continuous quality improvement. See also Case Example 25.

3.1. When Should a Patient Registry End?

3.1.1. Stopping an Experiment

The principles regarding rules for stopping a study mostly stem from the need to consider stopping an experiment. Because experiments differ from registries in crucial ways, it is important to distinguish between the issues involved in stopping an experimental study and in stopping a nonexperimental study.

In an experiment, the patient's treatment is determined by the study protocol, which typically involves random assignment to a treatment regimen. In a nonexperimental study, patients are treated according to the treatment protocol devised by their own clinician, typically uninfluenced by the study. In a randomized trial of a new therapeutic agent or a field trial for a vaccine, the size of the study population is ordinarily set in the study protocol, based on assumptions about the expected or hypothesized results and the study size needed to reach a reasonable scientific conclusion. Ordinarily this planned study size is based on power calculations, which require as input the criteria for statistical significance, the effect size anticipated, the baseline occurrence rate of the study outcome, and the relative size of the study arms. Because of inherent problems in relying on statistical significance for inference,[11,12] the study size preferably will be planned around estimation of effect and the desired level of precision. In a study intended to provide some reassurance about the safety of an agent, the study size may be planned to provide a specific probability that the upper confidence bound of a conventional confidence interval measuring an adverse effect would be less than some specified value, given a postulated value for the effect itself (such as no effect). In the latter situation, if no effect is anticipated, a power calculation is not only unreasonable but is not even possible, whereas planning a study on the basis of precision of estimation is always possible and always reasonable.

Stopping an experiment earlier than planned is an important decision that is typically made by an advisory group, such as a data safety and monitoring board, which is constituted to monitor study results and make decisions about early stopping. In a biomedical experiment, the investigator has a greater ethical obligation than in a nonexperimental study to safeguard the well-being of study participants. This is because the investigator is administering an intervention to study participants that is expected to affect the probability that study participants will experience one or more specific health outcomes.

Equipoise is a widely accepted (but, unfortunately, not universally accepted) ethical precept regarding human biomedical experimentation.[13] Equipoise requires that at the outset of the study, the investigator has a neutral outlook regarding which of the study groups would fare better. A strict interpretation of equipoise requires each of the study investigators to be in a state of equipoise. An alternative view, referred to as "clinical equipoise," is that equipoise can be achieved at the group level, with the enthusiasm of some investigators for the prospects of the study intervention being balanced by the skepticism of others.[14] Whichever interpretation of equipoise is adopted, most investigators agree that if equipoise becomes untenable as study results accumulate, the study should be stopped to avoid depriving some study participants of a potential benefit relative to what other participants receive.

For an advisory board to decide to stop a study early, there must be solid evidence of a difference between the groups before the planned study endpoint is reached. Such stopping decisions are usually based on ethical concerns, as scientific considerations would seldom dictate an early stop to a study that had been planned to reach a specific size. Advisory boards must base stopping decisions on analyses of accumulating study data, which are usually formally presented at regular meetings of the review board. Statistical concerns have been raised about biases that can arise from repeated analyses of accumulating data.[15] To offset these concerns, many experiments are planned with only a limited number of interim analyses, and the interpretation of study results takes into account the number of interim analyses.

3.1.2. Stopping a Fixed-Length Nonexperimental Study

Like experiments, most nonexperimental studies also have a fixed time for their conduct and a planned size that reflects goals analogous to those in experimental studies. Nevertheless, the ethical concerns that motivate stopping an experiment before its planned completion do not have a direct counterpart in nonexperimental studies. Nonexperimental studies do have ethical concerns, but they relate to issues such as data privacy, intrusive questioning, or excessive inducements for participation rather than to concerns about intervention in the lives of the participants. Although it is theoretically reasonable that an investigator could choose to stop a nonexperimental study for ethical reasons, those reasons would presumably relate to ethical problems that were discovered in the course of the study but were unrecognized at the outset rather than to an early conclusion regarding the study goal. The investigator in a nonexperimental study could learn, from an interim analysis, that the association between the exposure and the outcome under study was much stronger than anticipated. Unlike the experimental setting, however, the investigator in a nonexperimental study is not administering the exposure to any of the study subjects and thus has no responsibility to the study subjects regarding their exposure.

The discovery of an ethical problem during the conduct of a nonexperimental study is therefore possible but extremely rare. Because the findings from an interim analysis should not lead to discontinuation of a nonexperimental study, there is little motivation to conduct interim analyses for nonexperimental studies that have been planned with a fixed size and period of execution. If there is some considerable time value to the findings, such as to inform regulatory action, it might be worthwhile to conduct an interim analysis in a nonexperimental study to get an early appraisal of study findings. Unless there is an appropriate outlet for releasing interim findings, however, it is possible that early findings will not circulate beyond the circle of investigators. In most circumstances, such analyses are hard to justify in light of the fact that they are based on a smaller amount of data than was judged appropriate when the study was planned; thus the originally planned analysis based on all the collected data will still need to be conducted. Unless there is a clear public health case to publicize interim results, journal policies that require that published data have not been previously published may inhibit any release of preliminary findings to news media or to journals in the form of preliminary findings.

3.1.3. Stopping an Open-Ended Study

Although patient registries may be undertaken with a fixed length or size, or both, based on study goals relating to specific safety or efficacy hypotheses, many such studies are begun as open-ended enterprises without a planned stopping point. For example, patient registries without specific hypotheses may be undertaken to monitor the safety of patients receiving a novel therapy. The Antiepileptic Drug Pregnancy Registry, established in 1997, is an example of an open-ended registry that focuses on a set of specific endpoints (congenital malformations) among a subset of patients (pregnant women) taking a class of medications (antiepileptic drugs).[16] It has no fixed stopping point.

Measuring the frequency of rare endpoints demands large study sizes. Therefore, a monitoring system that includes rare endpoints may have to run for a long while before the accumulated data will be informative for low-frequency events. On the other hand, the lower the frequency of an adverse event, even one with serious consequences, the smaller is the public health problem that a relative excess of such events would represent.

Traditional surveillance systems are intended to continue indefinitely because they are intended to monitor changes in event frequency over time. For example, surveillance systems for epidemic infectious diseases provide early warning about outbreaks and help direct efforts to contain such outbreaks. In contrast, a patient registry is not a true surveillance system, since most are not intended to provide an early warning of a change in outcome frequency. Rather, most patient registries are intended to compile data on outcomes associated with novel treatments, to supplement the sparse data usually available at the time that these treatments are considered for approval by regulatory agencies. For example, a regulatory agency might mandate a patient registry as a condition of approval to supplement safety information that was submitted during the application process.

How long should such a registry continue? Although it is not possible to supply a general answer to this question, there is little reason to support a registry continuing indefinitely unless there is a suspicion that the treatments or treatment effects will change over time. Otherwise, the time should come when the number of patients studied suffices to answer the questions that motivated the registry. The Acyclovir Pregnancy Registry, which began in 1984, was stopped in 1999. Its advisory committee concluded: "The [Acyclovir Pregnancy] Registry findings to date do not show an increase in the number of birth defects identified among the prospective reports [of exposures to acyclovir] when compared with those expected in the general population. In addition, there is no pattern of defects among prospective or retrospective acyclovir reports. These findings should provide some assurance in counseling women following prenatal exposure [to acyclovir]."[17] The consensus was that additional information would not add materially to the information that had already been collected, and thus the registry was closed down.

To avoid uncertainty about the fate of an open-ended study, it would be sensible to formulate a specific goal that permits a satisfactory conclusion to data collection. Such a goal might be, for example, the observation of a minimum number of specific adverse events of some type. Even better would be to plan to continue data collection until the upper bound of a confidence interval for the rate or risk of the key outcome falls below some threshold or until the lower bound falls above a threshold. Analogous stopping guidelines could be formulated for registry studies that are designed with a built-in comparison group.

3.2. Decisions on Stopping and Registry Goals

Ideally, stopping decisions ought to evaluate data from a registry against its stated goals. Thus, the registry protocol or charter should include one or more specific and measurable endpoints against which to judge whether the project should continue or stop. Without that guidance, any decision to discontinue a registry may appear arbitrary and will be more readily subject to political considerations. In cases where there are no measurable endpoints to use in making the decision, it is important that any final reports or publications linked to the registry include a clear discussion of the reasons for stopping it.

Registry goals will vary according to the motivation for undertaking the project and the source of funding. Product-specific registries may be created as postapproval regulatory commitments. For products about which there are limited preapproval safety data, the wish for additional comfort about the product's safety profile can be translated into a measurable goal. Such a goal might be to exclude the occurrence of life-threatening or fatal drug-related events at a certain frequency. For example, the goal could be to establish a specified level of confidence that unexplained hepatic necrosis in the 3 months following drug exposure occurs in less than 1 patient in 1,000. Alternatively, the goal might be to provide a more precise estimate of the frequency of a previously identified risk, such as anaphylaxis. Ideally, this goal should be

formulated in specific numeric terms. With specific goals, the registry can have a planned target and will not be open ended.

If a registry study does not have a single or very limited set of primary objectives, a stopping point will be more challenging to plan and to justify. Even so, with measurable goals for some endpoints, it will be possible to determine whether the registry has achieved a core purpose and may lead to a reasonable stopping point. Conversely, a registry that fails to meet measurable goals and appears to be unable to meet them in a reasonable time is also a candidate to be stopped. For example, if the registry faces unexpectedly low patient accrual, it should be stopped, as was done with the Observational Familial Adenomatous Polyposis Registry Study in Patients Receiving Celecoxib.[18] This study enrolled only 72 patients in 4 years, out of a planned 200 during 5 years. Another reason to consider stopping is incomplete or poor-quality information. Poor-quality data are of particular concern when the data regard sensitive or illegal behavior, such as self-reported information on sexual practices.[19] Decisions about stopping a registry because of low enrollment or inadequate information are made simpler with clearly stated goals regarding both features of the study. The criteria for useful quantity and quality of information should be specified at the outset. How well the study meets the criteria can be assessed periodically during data collection.

A registry may outlive the question it was created to answer. For example, if use of the product is superseded by another treatment, the questions that drove the creation of the registry may no longer be relevant, in which case it may best be retired (see Case Example 42). For medical devices, for example, newer technology is continuously replacing the old, although safety issues for older technology may motivate continuing a registry of an outmoded technology. A related issue arises when the question of interest evolves as data collection proceeds. Stopping or continuing the registry depends on whether it can address the changing goal or goals. That, in turn, depends on whether the governance of the registry provides adequate flexibility to refocus the registry in a new direction.

The decision to stop a registry may also depend on mundane considerations such as cost or staffing. For long-running registries, eventually the value of new information may face diminishing returns. Some registries have central core staff, deeply committed to the registry, who serve as its historical memory. Departure of such individuals can cripple the registry's function, and a decision to stop may be appropriate. Similarly, a cohort of engaged investigators may disperse over time or lose interest in the registry. Funding sources may dry up, making it impossible for the registry to function at a level that justifies its continued existence.

A thorny question concerns how a registry can continue with altered ownership or governance. Suppose a registry is formed with multiple stakeholders, and one or more withdraws for the reasons described above. For example, when the implantable cardioverter defibrillator (ICD) registry was formed, it came about in response to a CMS Coverage with Evidence Development decision. The Heart Rhythm Society and the American College of Cardiology developed the registry with funding from industry to help institutions meet the need for registry participation for payment purposes, and they layered quality improvement and research goals onto that mandate.[20] The resulting registry was rapidly integrated into more than 2,000 institutions in the United States. If CMS determines that the ICD registry is no longer needed for its purposes, the registry must determine if it will continue as a quality improvement program and whether to

add other stakeholders and funding sources or participation drivers (such as manufacturers, insurers, or other government agencies such as FDA).

3.3. What Happens When a Registry Ends?

Stopping a registry might mean ceasing all information collection and issuing a final report. An intermediate decision that falls short of a full stop might involve ceasing to accrue new patients while continuing to collect information on existing participants. This step may be useful if the registry goals are in the process of changing. If a registry is to be stopped, the archiving rules should be checked and followed, so that those who need to consult the data for questions not fully addressed in reports or publications can get their answers later, provided that the charter of the registry allows it. Following German reunification in 1990, it was determined that the East German National Cancer Registry, which had received detailed reports on 2 million cancer cases from 1954 to 1990, was in violation of West German privacy laws, and the data were quarantined. In the more usual case, orderly archiving of the data in anticipation of later access should be part of the close-down procedure, in a manner consistent with the charter under which the data were collected.[21]

A slightly different scenario occurs when the registry has a single sponsor whose purposes have been achieved or determined to be unachievable and the sponsor decides to end the registry. Is there an obligation to patients or participating providers to continue the registry because some value (e.g., quality improvement, data for other comparisons) can still be derived? It is difficult to argue that the sponsor has an ongoing financial responsibility once the registry has achieved or failed to achieve its primary purpose, especially if this has been spelled out in the protocol and informed consent. Yet one can argue that, to the extent that it is feasible and affordable to engage other stakeholders in discussions of potential transitioning of the registry to other owners, this approach should be encouraged. Nontrivial issues of data ownership, property, confidentiality, and patient privacy would need to be satisfactorily addressed to make such transitions possible, and therefore it is always best to consider this possibility early on in registry planning. Both the National Registry of Myocardial Infarction (NRMI), sponsored by Genentech, Inc., and the OPTIMIZE-HF registry, sponsored by GlaxoSmithKline, successfully completed transitions to other organizations (American College of Cardiology and American Heart Association, respectively) when those registries were concluded, providing their participating hospitals with the ability to continue the quality improvement efforts begun under those registries.[22,23]

There is no clear ethical obligation to participants to continue a registry that has outlived its scientific usefulness. In fact, altering the purpose of a registry would be complicated unless the original registry operators were interested in doing so. For instance, if a registry is to be transferred, then it should be a restricted transfer (presumably a gift) to ensure that the permissions, terms, and conditions under which it was compiled continue to be satisfied. The participants should be notified and should determine if they will continue participation and allow their data to be used for this new purpose.

There are a few potential reasons to consider preserving registry data once the registry developers have determined that it should end. One reason is that the data may be capable of producing a recognized public health benefit that will continue if the registry does. Another situation may be that the registry has historical importance, such as a registry that tracks the outbreak of a novel infectious disease that may provide insight into the transmission of the disease, if not now, then sometime in the future. Longitudinal collections of data may also be useful for hypothesis generation.

In creating a registry, the investigators should plan what will happen to data when the registry ends. If a public health benefit might be realized from registry data, then archiving of registry data is a potential answer. Decisions must be made by the registry owners in careful consideration of other stakeholders, potential costs, and privacy and security concerns.

3.4. Summary of Considerations for Planning for the End of a Registry

Experimental studies, such as clinical trials or field trials, come with a high ethical burden of responsibility, which includes periodically reevaluating the ethical basis for continuing the trial in the light of interim results. Consequently, trials require interim analyses and data safety monitoring boards, which decide whether the study should be stopped for ethical reasons. In nonexperimental studies, there is much less motivation to conduct interim analyses because there is no ethical motivation to do so. There is also no reason to appoint a data safety monitoring board, although any study could appoint an external advisory board. If nonexperimental studies are planned to be of fixed length or fixed study size, they can be conducted as planned without interim analyses, unless the time value of an early, interim analysis is important enough to compensate for the added cost of conducting it and the tentativeness of the findings, which are based on only a subset of the planned study data.

If a patient registry is undertaken as an open-ended project without a fixed endpoint, it need not continue forever. Unlike true surveillance efforts, patient registries of novel therapies are not intended to monitor changes in occurrence rates over time. Rather, they are conducted to assemble enough data to evaluate associations that could not be evaluated with the limited data available at the time of new product approval. Therefore, reasonable goals should be set for the amount of information to be collected in such registries, based on specific endpoints of interest. These goals can and should be cast in specific terms regarding data quality, study enrollment, and precision of the estimates of specific measures that the registry is intended to describe.

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Case Examples for Chapter 14

Case Example 25. Determining When to Stop an Open-Ended Registry

Description	The Bupropion Pregnancy Registry was an observational exposure-registration and follow-up study to monitor prenatal exposure to bupropion and detect any major teratogenic effect.
Sponsor	GlaxoSmithKline
Year Started	1997
Year Ended	The registry closed to new enrollments on November 1, 2007, and continued to follow existing cases through March 31, 2008.
No. of Sites	Not applicable
No. of Patients	1,597

Challenge

Bupropion, an antidepressant with the potential for prenatal exposure, was labeled with a pregnancy category C by the U.S. Food and Drug Administration (FDA) due to prior animal data. The manufacturer established a prospective pregnancy registry to monitor pregnancy exposures to bupropion for any potential increased risk of congenital anomalies. Because the purpose of the registry was postmarketing safety surveillance, the duration of the registry was open ended. The registry had collected data on over 1,500 exposed pregnant women over 10 years when a potential signal suggestive of a bupropion-related increase in cardiovascular birth defects emerged.

Proposed Solution

The advisory committee reviewed the registry data to assess the potential signal. However, due to the potential bias from the large percentage of cases lost to followup (35.8 percent), retrospective reports, and incomplete descriptions of the reported cardiovascular defects, it was not possible to determine the credibility of the potential signal using registry data alone. Further, the sample size was not adequate to reach definitive conclusions regarding the absolute or relative risk of any specific birth defects in women using bupropion during pregnancy (as the registry was powered only to examine the rate of birth defects overall) and was unlikely to achieve its goal as structured.

The advisory committee recommended a study to expedite the accumulation of pregnancy outcome data among women exposed to bupropion during pregnancy. In response, a large, claims-based, retrospective cohort study was conducted. This study enrolled 1,213 women exposed in the first trimester and did not confirm a consistent pattern of defects (Cole et al., 2007). The prevalence of cardiovascular defects associated with first-trimester exposure to bupropion was 10.7 per 1,000 infants.

Results

The advisory committee reviewed the evidence and concluded that the signal did not represent an increased risk. The committee recommended discontinuation of the registry based on findings from the retrospective cohort and 10 years of surveillance through the registry. The committee took the position

that sufficient information had accumulated to meet the scientific objective of the registry. The high lost-to-followup rate was also taken into consideration. The registry closed to new enrollments on November 1, 2007, and continued to follow existing cases through March 31, 2008.

Key Point

In a registry without a specified end date or target size, it is important to periodically review the registry data to determine if the registry has met its scientific objectives and to ensure that the registry purpose is still relevant.

For More Information

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Case Example 26. Challenges in Transitions and Changes in Data Collection

Description	The Cystic Fibrosis Foundation (CFF) Patient Registry is a rare disease registry that collects data from clinical visits, hospitalizations, and care episodes to track national trends in morbidity and mortality, assess the effectiveness of treatments, and drive quality improvement in care for patients with cystic fibrosis (CF).
Sponsor	Cystic Fibrosis Foundation
Year Started	1986
Year Ended	Ongoing
No. of Sites	110 CFF-accredited care centers in the United States
No. of Patients	More than 26,000

Challenge

The CFF Patient Registry collects information on over 26,000 patients with cystic fibrosis who receive care at one of over 110 CFF-accredited care centers across the United States. The registry collects demographic and diagnostic information, lung function, nutritional status, respiratory microbiology, and other indicators of disease progression, as well as prescribed medications and hospitalizations. Registry data dating back to 1986 are used to track national trends in morbidity and mortality, to assess the effectiveness of treatments, and to drive quality improvement. The CFF Patient Registry has evolved through multiple iterations, including the most recent transition in 2010. This registry transition, prompted by the implementation of a new technology platform and the need to update and expand the data collection fields, imposed operational challenges on the CFF working group tasked with the registry

transition. Challenges included modifying data collection fields, mapping historical data, and ensuring usability for the sites.

Proposed Solution

Planning for the latest transition began in 2007, when CFF began searching for a new vendor with an FDA 21 CFR Part 11 compliant web platform. After selecting a vendor, CFF began the process of evaluating all data fields in the registry. Six working groups of subject matter experts were convened to review data fields from the existing registry and make suggestions for improvements, additions, and deletions (in the areas of genetics, pulmonology, microbiology, cystic fibrosis related diabetes, transplantation, and infant care/ambiguous diagnosis). CFF staff created an online prototype of the registry that allowed reviewers, including registry physicians and subject matter experts, to see and comment on all data fields and functions planned for the new registry platform. The recommendations of these groups were vetted by CFF staff in order to balance data entry burden for the care center staff and usefulness for future research.

After selecting data fields for the new version of the registry, focus shifted to designing online case report forms and mapping historical data into the new registry. For example, the old registry platform collected information on 81 distinct genotype mutations in addition to an "other, specify:" option. The genetics working group expanded the list of available mutation variables to 269, and data previously entered into the "other, specify:" field were mapped forward into these new mutation variables. Once mapping was complete, there were several iterative migrations of historical data into the new registry platform. CFF staff carefully audited the import process and identified errors prior to the launch of the live registry.

During a preliminary test period, users were able to log in to the new registry, populated with "dummy" data, and become acquainted with the new functionality, format, and questions in the registry. During a second test period, users viewed their actual patient data in the new registry, and helped to identify and resolve several minor errors in data migration. When the registry went live in April 2010, users were supported with online training manuals and videos, FAQ documents, Webinars, and live support.

Results

Three months after the successful addition of new fields and data migration to the new registry, a survey was distributed to all sites to solicit user feedback and identify areas for further change. The response rate was high, with 70% of users providing feedback on their experiences with the new platform. Responders ranged from new users to experienced sites, and results indicated that sites were still gaining familiarity with the new registry. Based on the survey responses, several modifications to the platform were made to improve the functionality of the system.

Key Point

The transition of the CFF Patient Registry to a new technology platform illustrates the importance of a well-planned registry transition. Early allocation of human and financial resources, collaboration with sites, and a realistic timeline allowed for stepwise development. This approach minimized disruption to users and ensured the integrity of the data migration process.

For More Information
www.cff.org

Case Example 27. Transitioning from Start-up to Ongoing Registry Funding With Public and Private Partners

Description	The Rheumatoid Arthritis Comparative Effectiveness Research (RACER) is a disease registry designed to assess comparative and cost effectiveness of existing and new biologic drug therapies for rheumatoid arthritis.
Sponsor	University of Pittsburgh; National Institutes of Health; Genentech, Inc.
Year Started	2010
Year Ended	Ongoing
No. of Sites	4 clinics in the Pittsburgh area
No. of Patients	More than 1,000

Challenge

RACER was established by researchers at the University of Pittsburgh to determine relative effectiveness of existing versus new and expensive biologic therapies for rheumatoid arthritis; compare biologic therapies in terms of mechanistic and biomarker measurements to predict optimal treatment; and test whether practical treat-to-target strategies can improve treatment management of the disease. Clinical outcomes assessed include disease activity, quality of life, function and work productivity, and biomarker and mechanistic outcomes including C-reactive protein, rheumatoid factor, and cyclic citrullinated peptide auto-antibody levels.

There is no protocol-mandated visit schedule, and providers determine the visit schedule appropriate for each patient. Registry data are extracted from the site's electronic health record (EHR) system and supplemented with patient-reported outcome (PRO) measures and some physician-reported measures at each visit. The laboratory values are measured using a blood sample collected at each visit.

Initial funding for the registry was provided through a grant from the National Institutes of Health (NIH) in 2009. This allowed for the registry to be launched, patients to be enrolled, and data collection to begin. However, the grant mechanism was for a finite period of two years, and university researchers saw value in continuing data collection. Researchers sought to continue registry operations and disseminate registry data and results to interested parties.

Proposed Solution

Prior to the end of NIH funding, the registry, which now had data on over 1,000 patients, began discussions with Genentech, Inc, a biotechnology company with two marketed biologics for rheumatoid arthritis. Initially, the discussions focused on data sharing and acquiring access to the registry dataset

with an intent to collaborate and generate real-world effectiveness of RA treatments. Although Genentech was not mandated by a regulatory agency to collect post-marketing data on their product, they expressed interest in being able to collect this data for scientific purposes with minimal investment in redundant or duplicative registry infrastructure. Genentech valued the work that RACER had done already, especially EHR integration, the collection of PROs and quality of life measures, and the potential for nested sub-studies within the larger registry database.

Discussions between the registry and Genentech turned to possible models for sustaining registry operations while granting Genentech access to the valuable comparative effectiveness data being collected by the registry.

Results

Plans are now in place to fully transition the funding of the registry to Genentech, after the original NIH contract has ended. Genentech will continue to have full access to registry data on an ongoing basis, but will have an arms-length relationship to the operations of the registry. The researchers and registry staff at the University of Pittsburgh will retain full control of registry operations and ownership of the registry dataset.

The University of Pittsburgh researchers and Genentech will meet regularly to collaborate on analyses, manuscripts, and abstracts. Work is currently being planned on a protocol for a nested sub-study to evaluate the relative efficacy of the four clinically relevant treatment options in patients failing their first TNF antagonist.

Key Point

Registries can benefit from public and private partners to secure funding during both the start-up and maintenance phases of the registry. Members of a public-private partnership may join and leave as funding becomes available and shared interests intersect. This partnership enables effective public-private collaboration to advance science using observational research.

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Case Example 28. Modifying a Registry Due to Changes in Standards of Care

Description	The GOLD reGISTry was a prospective, multi-center, 5-year global disease registry designed to collect information on patients with advanced and localized gastrointestinal stromal tumors. The registry collected diagnostic, treatment, and outcomes information in order to identify and compare practice patterns worldwide and assist practitioners in making treatment decisions as standards of care evolved.
Sponsor	Novartis Oncology
Year Started	2007
Year Ended	2012
No. of Sites	More than 200
No. of Patients	1653

Challenge

When it was launched in 2007, the 5-year GOLD reGISTry enrolled only patients with advanced gastrointestinal stromal tumors (GIST). This population was of interest to researchers because standards of care for advanced GIST were not as clearly defined and widely used as the standard of care for localized GIST, which was complete surgical excision. The sponsor expected that the outcomes data collected from advanced GIST patients would be valuable in helping to refine standards of care for these patients.

In 2008 and 2009, Gleevec®/Glivec® (imatinib mesylate) received FDA and EMEA approval for adjuvant use in localized GIST after tumor resection. This approval, combined with emerging clinical trial data, prompted new interest in collecting diagnostic, treatment, and outcomes information from patients with localized GIST.

Proposed Solution

The sponsor had selected a steering committee with engaged key opinion leaders (KOLs) who provided guidance for the study and encouraged flexibility in study design to allow for potential changes. In 2009, the steering committee convened and determined that the registry would begin collecting data on patients with localized GIST, in addition to those with advanced disease who were already enrolled in the registry. The study team drafted a protocol amendment to include the localized GIST population and allowing assessment of physician adherence to new clinical guidelines published by the European Society of Medical Oncology the same year. The data management and statistical analysis plans were also revised to allow for the incorporation of the new data.

Significant efforts were then directed at site engagement, including abstract submissions and publicity through the KOLs. The registry also maintained site interest through interim study summaries presented at professional congresses. The sponsor had limited monitoring resources available to accommodate the new patient population, so study designers developed a plan that utilized remote monitoring and training, reserving on-site visits for research-naïve sites or for-cause audits. This allowed monitors to focus on those sites that required more training and allowed these sites to gain clinical research experience in an observational study.

Results

The registry enrolled 1,653 patients in the two populations within four years: over 1000 with advanced GIST, and over 500 with localized GIST. The steering committee played an important role in the recruitment and retention of sites, highlighting the importance of the study through publications and interim summaries presented at scientific and professional congresses throughout the enrollment period. As the planned 5-year study period is completed, the sponsor is now in the process of locking the registry database in preparation for final analyses.

Key Point

Changes in standard of care can significantly impact the design of a study as new treatments are approved or new patient populations become of interest. Registry developers should anticipate that such changes might occur, and consider what aspects of the registry could be most impacted. A steering committee that is well regarded in the field and knowledgeable about the disease and treatment can provide significant guidance during registry transitions and keep sites engaged as the changes are implemented.

For More Information

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Section IV. Technical, Legal, and Analytic Considerations for Combining Registry Data with Other Data Sources

Chapter 15. Interfacing Registries with Electronic Health Records

1. Introduction

With national efforts to invest in electronic health record (EHR) systems and to advance the evidence base in areas such as effectiveness, safety, and quality through registries and other studies, it is clear that interfacing registries with EHRs will become increasingly important over the next few years. While both EHRs and registries utilize clinical information at the patient level, registries are population focused, purpose driven, and designed to derive information on health outcomes defined before the data are collected and analyzed. On the other hand, EHRs are focused on the collection and use of an individual patient's health-related information. While in practice there may be some overlap in functionality between EHRs and registries, their roles are distinct, and both are very important to the health care system. This chapter explores issues of interoperability and a pragmatic "building-block approach" toward a functional, open-standards–based solution. (In this context, "open standards" means non-proprietary standards developed through a transparent process with participation from many stakeholders. "Open" does not mean "free of charge" in this context—there may be fees associated with the use of certain standards.)

An important value of this approach is that EHR vendors can implement it without major effort or impact on their current systems. While the focus of this guide is on patient registries, the same approach described in this chapter is applicable to clinical research studies, safety reporting, biosurveillance, public health, and quality reporting. This chapter also includes case examples (Case Examples 29, 30, 31, and 32) describing some of the challenges and approaches to interfacing registries with EHRs.

An electronic health record refers to an individual patient's medical record in digital format. EHRs can be comprehensive systems that manage both clinical and administrative data; for example, an EHR may collect medical histories, laboratory data, and physician notes, and may assist with billing, interpractice referrals, appointment scheduling, and prescription refills. They can also be targeted in their capabilities; many practices choose to implement EHRs that offer a subset of these capabilities, or they may implement multiple systems to fulfill different needs. According to the Institute of Medicine (IOM), there are four core functionalities of an EHR: health information and data, results management, order entry and support, and decision support.[1]

The current EHR market in the U.S. is highly fragmented.[2] Until recently, the term EHR was broadly applied to systems that fall within a range of capabilities. However, since the passage of the American Recovery and Reinvestment Act of 2009 (ARRA), a transformative change has been underway, with a rapid increase in EHR adoption and a strong emphasis on standards and certification. Under ARRA, approximately $27 billion will be spent on incentives and other projects to support the adoption of EHRs

over the next several years.[3]. These incentives have spurred an increase in EHR implementation from 17 percent of U.S. office-based physicians in 2003 to an estimated 57 percent in 2011.[4]

To ensure that the EHRs implemented under the ARRA incentive program contain basic functionalities, new standards and a certification process have been developed. ARRA emphasizes the 'meaningful use' of EHRs by office-based physicians and hospitals. 'Meaningful use' refers to the use of certified EHR technology to "improve quality, safety, efficiency, and reduce health disparities; engage patients and families in their health care; improve care coordination; and improve population and public health while maintaining privacy and security."[5] ARRA describes the three main components of meaningful use as 1) "the use of a certified EHR in a meaningful manner, such as e-prescribing; 2) the use of certified EHR technology for electronic exchange of health information to improve quality of health care; and 3) the use of certified EHR technology to submit clinical quality and other measures."

The Office of the Secretary of Health and Human Services (HHS) has been charged under ARRA with setting standards and certification criteria for EHRs, with interoperability a core goal. Within HHS, the Office of the National Coordinator of Health Information Technology (ONC) is responsible for developing the standards and certification criteria for the meaningful use of EHRs. ONC is using a three-stage approach to developing criteria for meaningful use. Stage 1, released in 2011, sets basic standards for capturing data in an EHR and sharing data between systems. Stage 2, which is under development and scheduled for finalization in 2012, expands the basic standards to include additional functionality and to require reporting of more measures (e.g., quality of care measures, base functionality measures). Finally, Stage 3, to be released in 2015, will continue to expand on the standards in Stage 2. ONC is also developing an EHR certification program that will allow EHR vendors to demonstrate that their products contain sufficient functionality to support meaningful use.

Even with increasing standardization of EHRs, there are many issues and obstacles to achieving interoperability (meaningful communication between systems, as described further below) between EHRs and registries or other clinical research activities. Among these obstacles are limitations to the ability to use and exchange information; issues in confidentiality, privacy, security, and data access; and issues in regulatory compliance. For example, in terms of information interoperability and exchange, the Clinical Research Value Case Workgroup has observed that clinical research data standards are developing independently from certain standards being developed for clinical care data; that currently the interface between the EHR and clinical research data is ad hoc and can be prone to errors and redundancy; that there is a wide variety of modes of research and medical specialties involved in clinical studies, thus making standards difficult to identify; and that there are differences among standards developing organizations with respect to health care data standards and how they are designed and implemented (including some proprietary standards for clinical research within certain organizations). With respect to confidentiality, privacy, security, and data access, the Workgroup has pointed out that secondary use of data may violate patient privacy, and that protections need to be put in place before data access can be automated. In the area of regulatory compliance, it notes that for some research purposes there is a need to comply with regulations for electronic systems (e.g., 21 CFR Part 11) and other rules (e.g., the Common Rule for human subjects research).[6]

The new Federal oversight of EHR standards is clearly guided by the need to ensure that the EHRs that benefit from the market-building impact of the provider incentives will serve the broader public purposes

for which the ARRA funds are intended.[7] Specifically, the elusive goal that has not been satisfied in the current paradigm is the creation of an interoperable HIT infrastructure. Without interoperability, the HIT investment under ARRA may actually be counterproductive to other ARRA goals, including the generation and dissemination of information on the comparative effectiveness of therapies and the efficient and transparent measurement of quality in the health care system. Ideally, EHR standards will lay the groundwork for what the Institute of Medicine has called the "learning healthcare system."[8] The goal of a learning health care system is a transformation of the way evidence is generated and used to improve health and health care—a system in which patient registries and similar, real-world study methods are expected to play a very important role. Ultimately, the HIT standards that are adopted, including vocabularies, data elements, datasets, and technical standards, may have a far-reaching impact on how transformative ARRA will be from an HIT perspective.

2. EHRs and Patient Registries

Prior to exploring how EHRs and registries might interface, it is useful to clearly differentiate one from the other. While EHRs may assist in certain functions that a patient registry requires (e.g., data collection, data cleaning, data storage), and a registry may augment the value of the information collected in an EHR (e.g., population views, quality reporting), an EHR is not a registry and a registry is not an EHR. Simply stated, an EHR is an electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards, and that can be created, managed, and consulted by authorized clinicians and staff across more than one health care organization.[9] As defined in Chapter 1, a registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. Registries are focused on populations and are designed to fulfill specific purposes defined before the data are collected and analyzed. EHRs are focused on individuals and are designed to collect, share, and use that information for the benefit of that individual.

3. EHRs and Evidence Development

The true promise of EHRs in evidence development is in facilitating the achievement of a practical, scalable, and efficient means of collecting, analyzing, and disseminating evidence. Digitizing information can dramatically reduce many of the scalability constraints of patient registries and other clinical research activities. Paper records are inherently limited because of the difficulty of systematically finding or sampling eligible patients for research activities and the effort required to re-enter information into a database. Digitized information has the capacity to improve both of these requirements for registries, enabling larger, more diverse patient populations, and avoiding duplication of effort for participating clinicians and patients. However, duplication of effort can be reduced only to the extent that EHRs capture data elements and outcomes with specific, consistent, and interoperable definitions—or that data can be found and transformed by other processes and technologies (e.g., natural language processing) into standardized formats that match registry specifications. Besides enabling health care information to be more readily available for registries and other evidence development purposes, bidirectionally interoperable EHRs may also serve an efferent role of delivering relevant information from a registry back to a clinician (e.g., information about natural history of disease, safety, effectiveness, and quality).

4. Current Challenges in a Preinteroperable Environment

Data capture for research purposes, in general, can be challenging for clinicians. Of the many hospitals, health care facilities, and clinicians' offices that participate in studies, most have more than one data capture system; an estimated 17 percent have five or more.[10] In other words, hospitals and practices are changing their workflow to accommodate nonharmonized research demands. As a result, data capture can be awkward and time consuming for clinicians and their staff, especially for a registry in which a large number of patients may fit into a broad set of enrollment criteria. While some of this can be overcome without interoperable systems by means of uploads from these systems to registries of certain standard file formats, such as hospital or clinician office billing files, the need to re-enter data from one system to another; train staff on new systems; and juggle multiple user names, passwords, and devices presents a high barrier to participation, especially for clinicians, whose primary interest is patient care and who are often themselves resistant to change. The widespread implementation of EHRs that are not truly interoperable, coupled with the growth in current and future evidence development activities, such as patient registries, may ironically create significant barriers to achieving the vision of a national, learning health care system. In many respects, clinicians may be part of the problem, if they seek EHRs with highly customized interfaces and database schema rather than those that may be more amenable to interoperability.

Most EHRs are not fully interoperable in the core functions that would enable them to participate in the learning health care system envisioned by the IOM. This deficiency is directly related to a combination of technical and economic barriers to EHRs' adoption and deployment of standards-based interoperability solutions. There are more than 600 EHR vendors,[11] many of which provide heavily customized versions of their systems for each separate client. For some time there was significant interest in adding clinical research capabilities to already-implemented EHR systems,[12] but this so-called "Swiss army knife" approach did not prove to be technically or commercially effective. Issues ranged from standardization of core datasets to achieving compliance with U.S. Food and Drug Administration (FDA) requirements for electronic systems used in clinical research. And because there is no single national EHR, even if this were achievable it would not meet many registry purposes, since registries seek data across large, generalizable populations. In recent years, the industry has primarily turned back to pursuing an open-standards approach to interacting with, rather than becoming, specialized systems.[13] Appendix C describes many of the relevant standards and standards-setting organizations.

Even though many EHR systems are technically uniform, the actual software implementations are different in many ways. As a result, achieving interoperability goals (across the myriad of installed EHRs and current and future registries) through custom interfaces is a mathematical, and therefore economic, impossibility. (See Section 5 below.) An open-standards approach may be the most viable. In addition, as has been tested in many demonstrations and is slowly being incorporated by some vendors into commercial offerings, a user-configurable mechanism to enable the provider to link to any number of registries without requiring customization by the EHR vendor is also an important aspect of a scalable solution.

5. The Vision of EHR-Registry Interoperability

As the EHR becomes the primary desktop interface for physicians and other health care workers, it is clear that registries must work through EHRs in order for interoperability to be feasible. At the same time, there is a rapidly growing need for clinicians to participate in registries to manage safety, evaluate

effectiveness, and measure and improve quality of care. As a result, an EHR will need to serve as an interface for more than one registry simultaneously. In considering the need to interface EHRs with patient registries, it is useful to consider the specific purpose for which the patient registry is designed, and how an EHR that is interoperable with one or more registries might lessen the burden, barriers, or costs of managing the registries and other data collection programs. The following potential functions can be thought of with respect to a registry purpose:

- *Natural history of disease*: Identify patients who meet eligibility criteria, alert clinicians, present the relevant forms and instructions, capture uniform data, review the data prior to transmission, transmit data to the registry, and receive and present information from the registry (e.g., population views).
- *Effectiveness*: Identify patients who meet eligibility criteria, execute sampling algorithms, alert clinicians, present the relevant forms and instructions, capture uniform data, review the data prior to transmission, transmit data or analytics, and receive and present information from the registry (e.g., followup schedules, registry-wide results).
- *Safety*: Identify events for reporting through triggers, capture uniform data, review the data prior to transmission, transmit data, receive and present requests for additional information, and receive and present safety information from the registry.
- *Quality*: Identify patients who meet eligibility criteria, present the relevant forms and instructions, capture uniform data, review the data prior to transmission, transmit data to the registry for reporting, and receive and present quality measure information and comparators from the registry.

In a truly interoperable system, registry-specific functionality could be presented in a software-as-a-service or middleware model, interacting with the EHR as the presentation layer on one end and the registry database on the other. In this model, the EHR is a gateway to multiple registries and clinical research activities through an open architecture that leverages best-in-class functionality and connectivity. Registries interact across multiple EHRs and EHRs interact with multiple registries.

6. Interoperability Challenges

Interoperability for health information systems requires communication, accurate and consistent data exchange, and use of the information that has been exchanged. The two core constructs, related to communication and content, are *syntactic* and *semantic* interoperability.

6.1. Syntactic Interoperability

Syntactic interoperability is the ability of heterogeneous health information systems to exchange data. There are several layers of syntactic interoperability. First, the physical wiring must be in place, and the TCP/IP (Internet) is the de facto standard. On top of this, an application protocol is needed such as HTTP or SMTP. The third layer is a standard messaging protocol such as SOAP (Simple Object Access Protocol).[14] The message must have a standard sequence, structure, and data items in order to be processed correctly by the receiving system.

When proprietary systems and formats are used, the complexity of the task grows dramatically. For n systems, $n(n\text{-}1)/2$ interfaces are needed for each system to communicate with every other one.[15] For this reason, message standards are preferred. While this seems straightforward, an example portrays how, even for EHR to EHR communication, barriers still exist. Currently, the Health Level Seven (HL-7)

Version 2 message standard (HL-7 v2.5) is the most widely implemented standard among EHRs, but this version has no explicit information model; instead, it rather vaguely defines many data fields and has many optional fields. To address this problem, the Reference Information Model (RIM) was developed as part of HL-7 v3, but v3 is not fully adopted and there is no well-defined mapping between v2.x and v3 messages.

Syntactic interoperability assures that the message will be delivered. Of the challenges to interoperability, this is the one most frequently solved. However, solving the delivery problem does not guarantee that the content of the message can be processed and interpreted at the receiving end with the meaning for which it was intended.

6.2. Semantic Interoperability

Semantic interoperability implies that the systems understand the data that has been exchanged at the level of defined domain concepts. This "understanding" requires shared data models that, in turn, depend on standard vocabularies and common data elements.[16]

The National Cancer Institute's (NCI) Cancer Bioinformatics Grid (caBIG) breaks down the core components of semantic interoperability into information or data models, which describe the relationships between common data elements in a domain; controlled vocabularies, which are an agreed upon set of standard terminology; and common data elements, which use shared vocabularies and standard values and formats to define how data are to be collected.

The standardization of what is collected, how it is collected, and what it means is a vast undertaking across health care. Much work has been done and is continuing currently, although efforts are not centralized nor are they equally advanced for different medical conditions. One effort, called the CDASH (Clinical Data Acquisition Standards Harmonization) Initiative, led by the Clinical Data Interchange Standards Consortium (CDISC), aims to describe recommended basic standards for the collection of clinical trial data.[17] It provides guidance for the creation of data collection instruments, including recommended case report form (CRF) data points, classified by domain (e.g., adverse events, inclusion/exclusion criteria, vital signs), and a core designation (highly recommended, recommended/conditional, or optional). Version 1.0 was published in October 2008; v1.1 was published in January 2011 and included implementation guidelines, best practice recommendations, and regulatory references. It remains to be seen how widely this standard will be implemented in the planning and operation of registries, clinical trials, and postmarketing studies, but it is nonetheless an excellent step in the definition of a common set of data elements to be used in registries and clinical research.

Other examples of information models used for data exchange are the ASTM Continuity of Care Record (CCR) and HL7's Continuity of Care Document (CCD), which have standardized certain commonly reported components of a medical encounter, including diagnoses, allergies, medications, and procedures. The CCD standard is particularly relevant because it is one that has been adopted as part of CCHIT certification. The Biomedical Research Integrated Domain Group (BRIDG) model is an effort to bridge health care and clinical research standards and organizations with stakeholders from CDISC, HL7, NCI, and FDA. Participating organizations are collaborating to produce a shared view of the dynamic and static semantics that collectively define a shared domain of interest, (i.e., the domain of clinical and preclinical protocol-driven research and its associated regulatory artifacts).[18]

Even with some standardization in the structure and content of the message, issues exist in the use of common coding systems. For any EHR and any registry system to be able to semantically interoperate, there needs to be uniformity around which coding systems are to be used. At this time, there are some differences between coding systems adopted by EHR vendors and registry vendors. While it is still possible to translate these coding systems and/or "recode" them, the possibility of achieving full semantic interoperability is limited until uniformity is achieved.

The collection of uniform data, including data elements for risk factors and outcomes, is a core characteristic of patient registries. If a functionally complete standard dictionary existed, it would also greatly improve the value of the information contained within the EHR. But, while tremendous progress has been made in some areas such as cancer[19] and cardiology,[20] the reality is that full semantic interoperability will not be achieved in the near future.

Beyond syntactic and semantic interoperability, there are other issues that require robust, standardized solutions, including how best to authenticate users across multiple applications. Another issue is permission or authorization management. At a high level, how does the system enforce and implement varying levels of authorization? A health care authorization is specific to authorized purposes. A particular patient may have provided different authorizations to disclose information differently to different registries interacting with a single EHR at the same time, and the specificity of that permission needs to be retained and in some way linked with the data as they transit between applications. For privacy purposes, an audit trail also needs to be maintained and viewable across all the paths through which the data move. Security must also be ensured across all of the nodes in the interoperable system.

A third key challenge to interoperability is managing patient identities among different health care applications. See the Chapter 17 for further discussion.

7. Partial and Potential Solutions

Achieving true, bidirectional interoperability, so that all of the required functions for EHRs and patient registries function seamlessly with one another, is unlikely to be accomplished for many years. However, as noted above, it is critical that a level of interoperability be achieved to prevent the creation of silos of information within proprietary informatics systems that make it difficult or impossible to conduct large registries or other evidence development research across diverse practices and populations. Given the lack of a holistic and definitive interoperability model, an incremental approach to the successive development, testing, and adoption of open, standard building blocks toward an interoperable solution is the likely path forward. In fact, much has been done in the area of interoperability, and if fully leveraged, these advances can already provide at least a level of *functional interoperability* that could significantly ameliorate this potential problem.

From an EHR/registry perspective, functional interoperability could be described as a standards-based solution that achieves the following set of requirements:

> The ability of any EHR to exchange valid and useful information with any registry, on behalf of any willing provider, at any time, in a manner that improves the efficiency of registry participation for the provider and the patient, and does not require significant customization to the EHR or the registry system.

Useful information exchange constitutes both general activities (e.g., patient identification, accurate/uniform data collection and processing) and specific additional elements, depending on the purpose of the registry (e.g., quality reporting). Such a definition implies an open-standards approach where participation is controlled by the provider/investigator. To be viable, such a model would require that EHRs become certified to meet open standards for basic functional interoperability (the requirements of which would advance over time), but also allow EHRs the opportunity to further differentiate their services by how much they can improve the efficiency of participation.

While the goal of functional interoperability likely requires the creation and adoption of effective open standards, there have been several approaches to partially addressing these same issues in the absence of a unified approach. HIT systems, including some EHRs, have been used to populate registry databases for some time. The Society of Thoracic Surgeons (STS), the American College of Cardiology (ACC), and others utilize models that are based on a central data repository that receives data from multiple conforming systems, on a periodic basis, through batch transfers. Syntactic interoperability is achieved through a clear specification that is custom-programmed by the HIT systems vendor. Semantic interoperability is achieved by the publication of specifications for the data collection elements and definitions on a regular cycle, and incorporation of these by the systems vendors. Each systems vendor pays a fee for the specifications and for testing their implementation following custom programming. In some cases, an additional fee is levied for the ongoing use of the interface by the systems vendor. Periodically, as data elements are modified, new specifications are published and the cycle of custom programming and testing is repeated. While there is incremental benefit to the provider organizations in that they do not have to use multiple systems to participate in these registries, the initial and periodic custom programming efforts and the need to support custom interface requirements make this approach unscalable. Furthermore, participation in one registry actually makes participation in other, similar registries more difficult, since the data elements are customized and not usable in the next program.

The American Heart Association's Get With The Guidelines® program uses a Web services model for a similar purpose. The advantage of the Web services model is that the data are transferred to the patient registry database on a transactional basis (immediately), but the other drawbacks in custom programming and change management still apply. This program also offers an open standards approach through IHE RFD[21] or Healthcare Information Technology Standards Panel (HITSP) TP50, described below. These examples describe two models for using EHRs to populate registry databases; other models exist.

8. Momentum toward a Functional Interoperability Solution

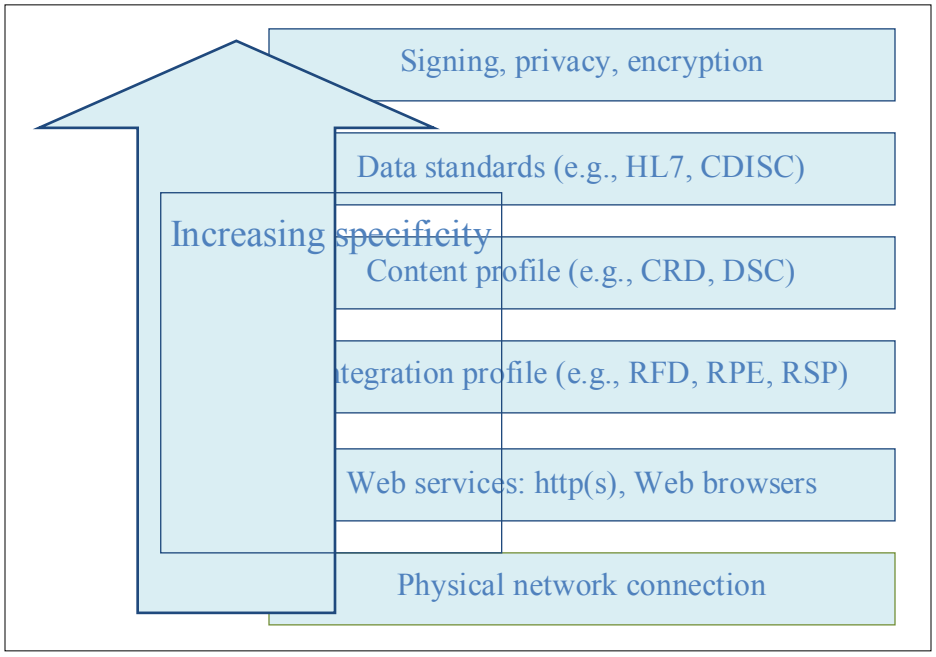
Significant momentum is already building toward adopting open-standard building blocks that will lead incrementally to functional interoperability solutions. For example, the EHR Clinical Research Value Case Workgroup has focused its use cases on two activities: achieving the ability (1) to communicate study parameters (e.g., eligibility information, CRFs) and (2) to exchange a core dataset from the EHR.[22] Others in the standards development community have taken a stepwise approach to creating the components for a first-generation, functional interoperability solution. As described below, this solution has already overcome several of the key barriers to creating an open, scalable model that can work simultaneously between multiple EHR systems and registries. Some of the issues that have been addressed through these efforts include: the need for flexibility in presenting a uniform data collection set that can be modified from time to time without custom programming by the EHR vendor; the need to leverage existing, standardized EHR data to populate portions of the data collection set; and the need to

be able to submit the data on a transactional basis to a registry, clinical trial, or other data recipient in a standard format.

Building-Block Approach. A building-block approach to the technical side of this issue is an effective and pragmatic way to build in increments and allow all players in the industry to focus on specific components of interoperability; early successes can then be recognized and used as the basis for the next step in the solution. This is a change from the earlier approaches to this issue, where the problem (and the solution) was defined so broadly that complete semantic interoperability seemed to be the only way to solve the problem; this proved overwhelming and unsupportable. Instead, a working set of industry-accepted standards and specifications that already exist can focus tightly on one aspect of interfacing multiple data capture systems, rather than considering the entire spread of issues that confound the seamless interchange between health care and research systems.

There are many different standards focused on different levels of this interface, and several different key stakeholders that create, work with, and depend on these standards (see Appendix C). A useful way to visualize these technical standards is to consider a stack where each building block is designed to facilitate one aspect of the technical interface between an EHR and a data collection system (Figure 8). The building blocks are modest but incremental changes that move two specific systems toward interoperability and are scalable to different platforms.

Figure 8. A Building-Block Approach to Interoperability



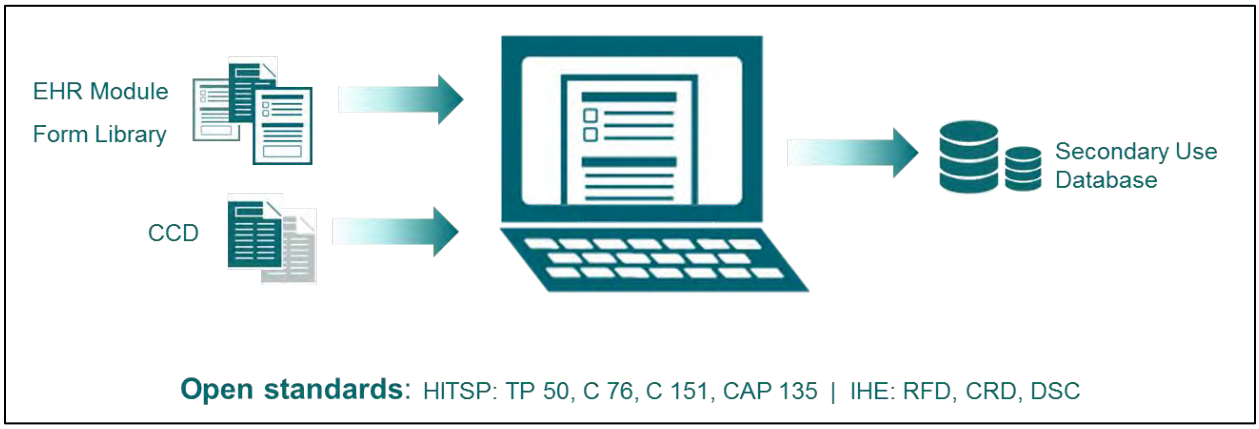
Note: *HL7 = Health Level Seven; CDISC = Clinical Data Interchange Standards Consortium; CRD = Clinical Research Data Capture; DSC = Drug Safety Content; RFD = Retrieve Form for Data Capture; RPE = Retrieve Protocol for Execution; RSP = Redaction Services Profile.*

This theoretical stack starts with the most basic technical components as the ground layers. Physical network connections, followed by Web services, secure hypertext transfer protocol (http), secure socket layer (SSL) communications protocol, and Web browsers create the foundation of the interoperability

structure. These standard technologies are compatible across most systems already, as part of the World Wide Web.

A standard integration profile, Retrieve Form for Data Capture (RFD), is the base of specific interoperability for health care data transfer, and takes advantage of the Web standards as a way to integrate EHRs and registry systems. RFD is a generic way for systems to interact. In a sense, RFD opens a circuit or provides a "dial tone" to allow an EHR to exchange information with a registry or other clinical research system. RFD was created and is maintained by Integrating the Healthcare Enterprise (IHE). It is also accepted under HITSP as TP50. Specifically, RFD provides a method for gathering data within a user's current application to meet the requirements of an external system (e.g., a registry). In RFD, as Figure 9 below shows, this is accomplished by retrieving a registry or other data collection form from a source; displaying it within the EHR system to allow completion of the form, with data validation checks, either through direct user entry or automated population from the EHR database; and then returning an instance of the data back to the registry system. Importantly, the EHR initiates the transaction.

Figure 9. Retrieve Form for Data Capture (RFD) Diagram



Once an EHR is RFD-enabled, it can be used for multiple use-cases. RFD opens a circuit and allows for information exchanges of different purposes, including registries and clinical trials, quality initiatives, safety, and public health reporting.[23]

Content profiles such as Clinical Research Data Capture (CRD) build the next level, allowing standard content defined within an EHR to be mapped into the data collection elements for the registry, eliminating duplicate entry for these defined elements. CRD and the Drug Safety Content (DSC) profiles, managed by IHE, build upon the IHE RFD integration profile. Correspondingly, HITSP C76, or Case Report Pre-Populate Component (for Drug Safety), leverages the HITSP TP50 retrieve form for data capture (RFD) transaction package.

CRD allows the functional interoperability solution to leverage standardized content as it becomes defined and available within EHRs. In other words, it is an incremental approach to leveraging whatever content has been rigorously defined and resident within the EHR and is also usable and acceptable to the registry (i.e., content that matches some portion of the registry's defined data elements and definitions). To the extent that these data reside in a common format, they can be used for autopopulation of the

registry forms without custom programming. CRD leverages the Continuity of Care Document (CCD), an HL7 standard. In this scenario, the CCD is generated by the EHR to populate a case report form. Only the relevant data from the CCD are used by the registry, as determined by the registry system that is presenting the form. Alternatively, CRD specifies that CDASH, a CDISC standard for data collection elements, may be used as the content message to prepopulate the case report form.

9. The Next Increment

As the basic components of functional interoperability are being tested and implemented, more attention is being focused on the next increments of the building-block approach. The important challenges to be addressed include: patient identification/privacy protection; the potential and appropriate use of digital signatures; other related and emerging profiles, such as querying the EHR for existing data through the Query for Existing Data (QED) profile; and transferring process-related study information as captured in the study protocol (Retrieve Protocol for Execution [RPE]). More extensive work in data mapping and the development of use cases around content are also needed.

9.1. Patient Identification/Privacy Protection

Patients within the context of clinical care are identified by a patient identifier, usually referred to as a medical record number. When these patients participate in a registry, they will also have a patient identifier within the context of the registry's programs. In some cases, where explicit authorization has been obtained, the medical record number may be shared across programs and can be used as a common identifier that links the patient across systems. In other cases, there is a need to anonymize the patient identifier. In the latter situation, infrastructure can be deployed to create unique, anonymized patient identifiers that serve to protect the patients' identity and facilitate secure patient identity management (e.g. Patient Identifier Cross-Referencing [PIX]).[24]

Beyond anonymizing, it also may be desirable to maintain a cross-referencing of patient identifiers or aliases across multiple systems so that the medical record number within the EHR can be linked back to the identifier within the registry or clinical trial without revealing the patient identity. Pseudonymization is a procedure by which all person-related data are replaced with one artificial identifier that maps one-to-one to the person.[25] Pseudonymization allows for additional use cases where it is necessary to link a patient seen in different settings (such as linking back to source records for additional information or monitoring).[26] See Chapter 17 for a more detailed discussion of this topic.

9.2. Digital Signatures

Certain registry purposes (such as regulatory reporting) require electronic signatures; for example, when the clinician or investigator attests to the completeness and accuracy of information being submitted for a research purpose. The current paradigm is the physical or electronic signing by the investigator of a paper or electronic case report form. The potential and appropriate use of digital signatures may further broaden the set of use cases by which EHRs may be utilized for secondary purposes. Other approaches to facilitating identity management, signing, and verification, such as Private Key Infrastructure (PKI), provide advantages in terms of nonrepudiation and detection of tampering. In the next wave of the interoperability effort, it will be important to define those scenarios that will require the strength of an enhanced digital signature.

9.3. Other Related and Emerging Efforts

As the building blocks of interoperability develop, additional flexibility will be gained as the registry and EHR can more fully communicate in a common language, both to request more clinical data and to provide the EHR with more information on the workflow requirements of the registry or other study protocol. These requirements point to other work being done to address these issues. Below are three examples from IHE profiles, some of which are under development by the Quality, Research, and Public Health (QRPH) Domain:

- **Retrieve Protocol for Execution (RPE)**. This integration profile allows an EHR to retrieve a protocol or a complex set of clinical research instructions necessary to fulfill the specified requirements of a protocol. The availability of these definitions and a set of transactions defined by RPE can: provide an EHR with content that may be used to identify patients for a research program based on defined inclusion/exclusion criteria, manage the patient visit schedule and appropriate case report forms or assessments that need to be completed in the appropriate sequence, and/or assist with other clinical activities such as ordering protocol-specified tests or laboratory reports.[27] RPE eliminates the need to manually enter data in two places (an EHR and an EDC collecting data for clinical research), resulting in a lower user burden on sites participating in research, as they are able to contribute EHR data to research protocols without leaving their EHR session.
- **Redaction Services Profile (RSP).** This integration profile addresses the privacy concerns around the exchange of electronic health data. It provides a way to redact certain data (e.g., personal identifiers) before transmitting that data from one system to another (e.g., from an EHR to a QRPH system), and acts as a "safety net" by ensuring that only the necessary and specified data is transmitted. In addition to this function, it also records and maintains an audit trail of the transmissions it facilitates, to support data quality processes.[28]
- **Drug Safety Content (DSC).** This content profile from the QRPH Domain details which data (and in what format) should be used in the RFD pre-population transaction between the Form Manager and Form Filler. It is specifically used for reporting adverse events and other data related to drug safety.[29]

9.4. Data Mapping and Constraints

While the efforts described above continue to expand the use of electronic medical record data for a variety of secondary purposes, it is clear that clinical and research teams, standards, and terminologies need to be further harmonized to maximize the benefits of information sharing across the variety of clinical and research systems. Effective and efficient management requires that harmonization efforts are furthered among vendors and standards organizations. It also requires that use cases continue to be honed and explicitly defined so that new clinical document constraints can be applied as necessary for each specified use case. Use cases will range across study types and across purposes, including drug safety, biosurveillance, and public health. Each clinical document constraint should strive to capture and deliver the information necessary to fully support the level of information sharing required by the scenario that maximizes both the efficiency of the clinical care/research workflow and the value of previously collected relevant data.

10. What Has Been Done

A number of efforts have demonstrated success in implementing several of the aforementioned building-block standards to achieve functional interoperability for registry purposes, including safety, effectiveness, and quality measurement. In one case, a registry focused on effectiveness in pain management was made interoperable with a commercial EHR using RFD communication.[30] In a second case, the Adverse Drug Event Spontaneous Triggered Event Reporting (ASTER) project,[31] interoperability was achieved for the purpose of reporting adverse event information to the Food and Drug Administration (FDA). (See Case Example 32.) In a third case, a commercial EHR was made interoperable with a quality reporting initiative for the American College of Rheumatology (ACR),[32] and to a Physician Quality Reporting Initiative (PQRI) Registry for reporting data to the Centers for Medicare & Medicaid Services (CMS).[33] In each case, both the registry and the EHRs were able to exchange useful information and decrease the effort required by the participating physicians.

11. Distributed Networks

It should be noted that the models of interoperability discussed above presume that data are shared between a distributed EHR and a patient registry (or another recipient such as a regulatory authority or a study sponsor). Alternative models may leave all data within the EHR but execute analyses in a distributed fashion and aggregate only results. To effectively accomplish distributed analyses requires either semantic interoperability or the ability to map to a conforming database structure and content, as well as the sophistication of a large number of EHR systems to run those types of queries in a manner that does not require providers to customize or program their systems. Several groups are advancing these concepts, and they may eventually prove to be very suitable for particular registry purposes (e.g., safety or public health surveillance).

PopMedNet™ is one example of a distributed network model.[34,35,36] PopMedNet is a software application that enables the creation of a distributed health data networks and supports the operation and governance of these networks.[37] Through the application, researchers can create and distribute queries to network data partners, who can then execute the queries and return the aggregate results to the researchers. Data partners retain control of their data and are able to review queries before responding. The PopMedNet application is designed to support a variety of data networks; therefore, the application does not use a specific data model or governance structure, but instead allows each data network to customize its implementation.

Currently, the PopMedNet application is being used for several research projects, including the Mini-Sentinel project, the Scalable PArtnering Network for CER: Across Lifespan, Conditions, and Settings (SPAN), and the Population-based Effectiveness in Asthma and Lung Diseases (PEAL) project. The Mini-Sentinel project is designed to facilitate the development of an active surveillance system for monitoring the safety of medical products. SPAN uses the application to conduct comparative effectiveness research in obesity and attention deficit hyperactivity disorder. The PEAL project aims to understand factors that affect prescribing and adherence to asthma medications.[38] The software application initially was developed by the HMO Research Network Center for Education and Research on Therapeutics and the University of Pennsylvania under contract to the Agency for Healthcare Research and Quality (AHRQ) as part of the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program. Additional development was supported by AHRQ and the Food and Drug Administration's Mini-Sentinel project.[39]

12. Summary

Achieving EHR–registry interoperability will be increasingly important as adoption of EHRs and the use of patient registries for many purposes both grow significantly. The linkage of registries with HIEs is also important, as HIEs may serve as data collection assistants with which registries may need to interact.[40] Achieving interoperability between these data sources is critical to ensuring that the massive HIT investment under ARRA does not create silos of information that cannot be joined for the public good.[41] Such interoperability should be based on open standards that enable any willing provider to interface with any applicable registry without requiring customization or permission of the EHR vendor. Interoperability for health information systems requires accurate and consistent data exchange, along with use of the information that has been exchanged. In addition, care must be taken to ensure that integration efforts comply with legal and regulatory requirements for the protection of patient privacy.

While full semantic interoperability remains distant, a great deal of useful work has and is being done. For example, the adoption of open standards such as HITSP TP50, C76 and IHE RFD, CRD, and DSC greatly enhance the ability of EHRs and registries to function together and reduce duplication of effort. *Functional interoperability* is a goal that can be achieved in the near term with significant gains in improving workflow and reducing duplication of effort for providers and patients participating in registries. The successive development, testing, and adoption of open-standard building blocks, which improve functional interoperability and move us incrementally toward a fully interoperable solution, is a bridging strategy that provides benefits to providers, patients, EHR vendors, and registry developers today.

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Case Examples for Chapter 15

Case Example 29. Using System Integration Software to Capture Registry Data from Electronic Health Records

Description	The PINNACLE Registry is an office-based, ambulatory cardiology quality improvement registry. The registry collects data to facilitate performance metric evaluation in coronary artery disease, atrial fibrillation, hypertension, and heart failure.
Sponsor	American College of Cardiology Foundation (ACCF)
Year Started	2007
Year Ended	Ongoing
No. of Sites	Over 500
No. of Patients	Over 2,000,000 patient records

Challenge

Collection of registry data in an outpatient setting can be challenging. Sites wishing to participate in the PINNACLE Registry can choose to collect and submit their data on paper or electronically. Paper data collection (i.e., having a dedicated clinical abstractor manually abstract data from an existing medical record into a data collection form) can be disruptive to practice workflow. This method also requires such a significant investment in human resources (from both the site and the registry) that the PINNACLE Registry is no longer accepting new sites that submit data on paper.

Electronic data submission involves directly abstracting relevant registry information from electronic health records (EHRs). The registry certified two EHR vendors as fully compatible and able to submit data automatically to the registry, which minimizes the data entry burden on sites. However, many potential sites use other EHRs, and the lack of standardized terminology and data collection formats among the many EHR options available to practices makes it challenging to provide an integration solution that serves the largest possible number of sites.

Proposed Solution

Recognizing these challenges, the American College of Cardiology Foundation (ACCF) partnered with a technology partner to develop the PINNACLE Registry System Integration Solution (SI). The SI is comprised of 1) a Microsoft SQL based database which stores registry measures and the data mapping specifications for the relevant EHR, 2) a .NET 4.0-based Windows Service which interfaces with the EHR and extracts the relevant registry data, and 3) a .NET 4.0-based Windows Client which configures the data extractions and adjusts mappings to suit the practice's specific use of the EHR. The SI is compatible with any EHR system, including those that have been highly customized at the practice level.

The registry team works with potential sites to complete a technical questionnaire, providing details about the practice's technical environment and EHR system. The SI software is then installed on the practice's server, is programmed to collect registry data elements that are already captured in the

existing EHR system, and exports the data directly to the registry database. The primary human resource requirement is from the practice's information technology team who work with the technology partner to install the solution on the practice's server.

Results

Currently, 80% of sites participating in the PINNACLE Registry use the SI to submit their data. The SI software has been successfully installed and implemented at 396 sites, which combined use 19 different EHR products. Installation and data mapping is currently underway at sites using 14 other EHR products.

The PINNACLE Registry System Integration Solution allows for the collection of registry data with minimal disruption of practice workflow. By eliminating the need for manual chart abstraction and data entry, some barriers to practice participation are removed. However, this means that if data are missing in the electronic health record, the same data will be missing in the registry record. Because of the lack of standardization in electronic health record systems, the SI solution does require time and resources during the startup phase to implement in a particular practice. Until such standards exist, the SI solution is a viable solution for capturing registry data with minimum workflow disruption and minimum human capital commitment.

Key Point

Extracting registry data directly from ambulatory EHRs can reduce the data entry burden on participating sites. A software solution that executes this extraction automatically may take time to set up initially, but minimizes workflow disruption during continued registry participation. An integrated solution that is flexible enough to accommodate many different EHR vendors and levels of customization can reduce barriers to registry participation for many sites.

For More Information

https://www.pinnacleregistry.org/Pinnacle/PINNACLERegistry/DataCollection.aspx

Case Example 30. Creating a Registry Interface to Incorporate Data from Multiple Electronic Health Records

Description	The MaineHealth Clinical Improvement Registry (CIR) is a secure Web-based database system that provides a tool for primary care physicians in the outpatient setting to consolidate and track key clinical information for preventative health measures and patients with common chronic illnesses.
Sponsor	The project is the result of a collaboration between Maine Medical Center (MMC) Physician-Hospital Organization, MaineHealth, and MMC Information Services.
Year Started	2003
Year Ended	Ongoing
No. of Sites	106 primary care practices (450 providers)
No. of Patients	More than 200,000

Challenge

A physician-hospital organization (PHO) developed a Web-based patient registry to improve quality of care and track patient outcomes across a large network of physicians. Many practices in the network used electronic health records (EHRs) and did not have sufficient staff to enter patient data a second time into a registry. In addition, the practices used a wide range of EHRs, and each had unique technical specifications. The registry needed a technical integration solution to reduce the data entry burden on practices that used EHRs, but, due to resource limitations, it could not develop customized interfaces for each of the many different EHRs in use.

Proposed Solution

The registry elected to allow practices to submit data from their EHRs to the registry in a one-way data transfer. An interface was written against an XML specification. Practices wishing to participate in the registry without doing direct data entry must be able to export their data in a file that conforms to this specification (although HL7 files are accepted when necessary). Data transfers occur on a schedule determined by each site—some send their data in real time while others send on a monthly basis.

Once data files are received by the registry, registry staff members review each portion of the data (demographics, vaccinations, office visits, etc.) before signing off on the file and incorporating the data into the registry. Extensive error checking and validation are completed during the initial specification phase to minimize the amount of manual data checking needed during each transfer. The validation phase involves both technical staff and quality improvement staff at the practices to ensure that the data are transferred and mapped correctly into the registry database.

Results

Of the 106 primary care practices participating in the registry, about 60 percent enter data directly into the registry, and about 40 percent contribute data via XML transfer. The organization and management of this initiative have required strong internal support from the registry and from participating practices. Management teams and technical resources were needed during the startup phase and continue to be essential as more practices contribute data via XML transfer.

Key Point

Technical interface solutions between registries and EHRs can be successful, but require a robust organizational commitment from the registry sponsor and participating sites to provide the necessary resources during the setup and launch phases.

For More Information

http://www.mmcpho.org/technology/mainehealth_clinical_improvement_registry_cir/.

Case Example 31. Technical and Security Issues in Creating a Health Information Exchange

Description	The Oakland Southfield Physicians Quality Registry is a practice-based registry designed to promote health outcomes and office efficiencies, and to identify early interventions and best practices in primary care practices. The registry integrates and exchanges health information from many sources through the Oakland Southfield Physicians Health Information Exchange (OSPHIE).
Sponsor	Oakland Southfield Physicians
Year Started	2006
Year Ended	Ongoing
No. of Sites	150
No. of Patients	Network covers more than 250,000 patients

Challenge

In 2006, the practice association launched a registry to improve the quality of care in its primary care practices. However, the association quickly realized that it needed to integrate and exchange health information from multiple sources, such as payer claims, pharmacy claims, practice management systems, laboratory databases, and other registry systems, on behalf of over 150 primary care practices.

Proposed Solution

To support this requirement, the practice association constructed a health information exchange (HIE). The HIE is a data warehouse made up of multiple data sources that facilitates the collaborative exchange of health information with a network of trading partners and then integrates the patient disease registry data with a wide range of supplemental clinical information. The HIE allows the registry to securely exchange data with trading partners (third party payers, laboratories, hospitals, registry systems, etc.) via a variety of methods and in a variety of structures. By pushing information both to the registry system and to other systems, the HIE eliminates duplicate data entry. Data transfers occur at established intervals, based on record updates or availability of information.

A key aspect of the system is the master patient and physician index, which allows data from various sources to be linked to the proper patient. Prior to import, data received in the registry are validated against a master patient and physician index for accuracy.

Results

Through data sharing with the Oakland Southfield Physicians (OSP) registry, the practice association has been able to facilitate the alignment of multiple data sources, with evidence-based care guidelines available at point of care—a value partnership striving to improve health outcomes as well as the efficient access to key health care data points. This solution relies on building trust between trading partners in support of both the secure transfer of information and recommended use.

The HIE has successfully incorporated data from practice management systems, laboratory providers, an e-prescribing system, a registry system, and third-party payers (medical and pharmacy claims detail). Relevant data are currently transmitted on behalf of the participating physicians in a real-time capacity

from the HIE to both the registry system and the e-prescribing system. The data warehouse also generates monthly "gaps-in-care reports" for physician clinical quality review and patient outreach.

Key Point

An HIE may be a useful tool for integrating and exchanging data between registries and other systems. When integrating data from many sources, a master patient and physician index can be a critically important tool for ensuring that the incoming data are linked to the appropriate patient.

For More Information

http://www.ospdocs.com/OSP+Advantage/Clinical+Quality+Registry-21.html

Case Example 32. Developing a New Model for Gathering and Reporting Adverse Drug Events

Description	The Adverse Drug Event Spontaneous Triggered Event Reporting (ASTER) study uses a new approach to the gathering and reporting of spontaneous adverse drug events (ADEs). The study was developed as a proof of concept for the model of using data from electronic health records to generate automated safety reports, replacing the current system of manual ADE reporting. The goals are to reduce the burden of reporting and provide timely reporting of ADEs to regulators.
Sponsor	Brigham and Women's Hospital, Partners Healthcare, CDISC, CRIX International, Claricode, and Pfizer Inc.
Year Started	Pilot launched in 2008
Year Ended	Pilot ended in 2009
No. of Sites	N/A
No. of Patients	N/A

Challenge

Health care data are rapidly being translated into electronic formats; however, to date, safety reporting has not taken full advantage of these electronic data sources. The spontaneous adverse event reporting system, which relies on reports submitted manually by health care professionals, is still the primary source of data on potential adverse drug events (ADEs). However, the availability of large amounts of data in electronic formats presents the opportunity to rethink the spontaneous adverse event reporting system. A new model could take advantage of the increasing availability of electronic data and improving technology to automate the process of gathering and reporting ADEs. The goals of automated ADE reporting are to reduce the burden of reporting on physicians, improve the frequency with which ADEs are reported, and increase the timeliness and quality of ADE reports.

An automated model, however, must overcome many challenges. The system must be scalable, must incorporate data from many sources, and must be flexible enough to adapt to the needs of many diverse

groups. The model must address point-of-care issues (such as burden of reporting), data exchange standards (so that the data are interpretable and valid), and processes for reviewing the ADE reports.

Proposed Solution

The Adverse Drug Event Spontaneous Triggered Event Reporting (ASTER) study attempted to address these challenges and demonstrate the potential viability of an automated model for facilitating the gathering and reporting of ADEs. ASTER allowed data to be transferred from an electronic health record (EHR) to an adverse event case report form and submitted directly to the U.S. Food and Drug Administration (FDA) in the format of an individual case safety report (ICSR). The process of gathering and reporting ADEs through ASTER involves four steps based on the open-standard "Retrieve Form for Data Capture (RFD)":

1. A physician indicates in the EHR that a drug was discontinued due to an ADE.
2. The system immediately generates an ADE report form that is prepopulated with demographic, medication, vital signs, and laboratory data. The physician sees the form in the EHR.
3. The physician enters a small amount of additional data, such as outcomes of the adverse event, to complete the AE report form.
4. The form is then processed by a third-party forms manager, who sends it to FDA as a reported spontaneous adverse event from the physician, in a standard format.

Results

The pilot phase of ASTER began in 2008. The goal of this phase was to demonstrate proof of concept for the new model. Specifically, it was hypothesized that (1) if an EHR could help a clinician identify potential adverse events, and (2) if the burden of completing an adverse event form was significantly reduced, then the rate of reporting of spontaneous adverse events to FDA could be significantly increased. ASTER recruited 26 physicians, 91 percent of whom had not reported an adverse event to FDA in the prior year. Following implementation, more than 200 events were reported over a period of three months.

There are still many questions that need to be answered before the ASTER model could become more widely used in the United States. For example, initial findings from ASTER suggest that an increased number of events are being reported using this model; this creates a need for the receiver of the reports (i.e., FDA) to have sufficient capacity to respond to the reports. Also, the fields that are captured in the ASTER model are based on the paper form fields. Moving to a truly digital system may require a change in the data collected to better align with the way data are collected in electronic formats. In 2012, the FDA published the results of a quality assessment of the data they received during the ASTER pilot. While the assessment noted the potential value of such an automated reporting system, it also provided suggestions for improving the quality and utility of the data. In the pilot, users selected an ADE description from a predefined list of relatively broad terms; the authors of the FDA report suggested that either this list be amended to include standardized terms for these clinical events, or users enter free text to describe the ADE, which could later be coded. Other suggestions included the implementation of real-time edit checks to catch illogical data such as an ADE date that precedes the initiation date of the suspected drug.

This ADE reporting model is now being expanded to include adverse events related to medical devices. The "ASTER-D" project, focused on device safety reporting, builds upon the ASTER concepts. A pilot study is currently underway, sponsored by the FDA's Center for Devices and Radiological Health (CDRH).

Key Point

New models for gathering and reporting ADEs may be able to leverage electronic health data and emerging technologies to both improve the timeliness of reporting and reduce the burden of reporting on health care professionals.

For More Information

http://www.asterstudy.com

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Chapter 16. Linking Registry Data with Other Data Sources to Support New Studies

1. Introduction

The purpose of this chapter is to identify important technical and legal considerations and provide guidance to researchers and research sponsors who are interested in linking data held in a health information registry with additional data, such as data from claims or other administrative files or from another registry. Its goals are to help investigators find an appropriate way to address their critical research questions, remain faithful to the conditions under which the data were originally collected, and protect individual patients by safeguarding their privacy and maintaining the confidentiality of the data under applicable law.

There are two equally important questions to address in the planning process: (1) What is a feasible technical approach to linking the data, and (2) Is the linkage legally feasible under the permissions, terms, and conditions that applied to the original compilations of each dataset? Legal feasibility depends on the applicability to the specific purpose of the data linkage of Federal and State legal protections for the confidentiality of health information and participation in human research, and also on any specific permissions obtained from individual patients for the use of their health information. Indeed, these projects require a great deal of analysis and planning, as the technical approach chosen may be influenced by permitted uses of the data under applicable regulations, while the legal assessment may change depending on how the linkage needs to be performed and the nature and purpose of the resulting linked dataset. Tables 22 and 23, respectively, list regulatory and technical questions for the consideration of data linkage project leaders during the planning of a project. The questions are intended to assist in organizing the resources needed to implement the project, including the statistical, regulatory, and collegial advice that might prove helpful in navigating the complexities of data linkage projects. This chapter presumes that the investigators have identified an explicit purpose for the data linkage in the form of a scientific question they are trying to answer. The nature of this objective is critical to an assessment of the applicable regulatory requirements for uses of the data. Investigators should assign the goal of the data linkage project to one of the following categories of health care operations as defined by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule: including: health care quality-related activities, public health practice, research, or some combination of these purposes. If research is one purpose of the project, then the Common Rule (Federal human subjects protection regulations) is likely to apply to the project. More information on HIPAA and the Common Rule is provided in Chapter 7.

The application of the HIPAA Privacy and Security Rules depends on the origins of the datasets being linked, and such origins may also influence the feasibility of making the data linkage. Investigators should know the source of the original data, the conditions under which they were compiled, and what kinds of permissions, from both individual patients and the custodial institutions, apply to the data. Health information is most often data that have two sources: individual and institutional; these sources may have legal rights and continuing interests in the use of the data.

It is important to be aware that the legal requirements may not remain stable and that the protections limiting the research use of health information are likely to change in response to continued development of electronic health information technologies.

This chapter provides eight sections focusing on core issues in three major parts: Technical Aspects of Data Linkage Projects, Legal Aspects of Data Linkage Projects, and Risk Mitigation for Data Linkage Projects. The Technical Aspects of Data Linkage Projects section discusses the reasons for and technical methods of linking datasets containing health information, including data held in registries. It should be noted that this list of techniques is not intended to be comprehensive, and the techniques presented have limitations for certain types of studies. The reader is referred to the published literature on linkage for alternative techniques. The Legal Aspects of Data Linkage Projects section defines important concepts, including the different definitions of "disclosure" as used by statisticians and in the HIPAA Privacy Rule. This section also discusses the risks of identification of individuals inherent in data linkage projects and describes the legal standards of the HIPAA Privacy Rule that pertain to these risks. Finally, the Risk Mitigation for Data Linkage Projects section summarizes both recognized and developing technical methods for mitigating the risks of identification. In addition, Appendix D consists of a hypothetical data linkage project intended to provide context for the technical and legal information presented below. Case Examples 33, 34, 35, and 36 describe registry-related data linkage activities. Chapter 18 provides information on analyzing linked data sets. While some of the concepts presented are applicable to other important nonpatient identities that might be at risk in data linkage, such as provider identities, those issues are beyond the scope of the discussion below.

2. Technical Aspects of Data Linkage Projects

2.1. Linking Records for Research and Improving Public Health

Data in registries regarding the health of individuals come in a wide variety of forms. Most of these data have been gathered originally for the delivery of clinical services or payment for those services, and under promises or legal guarantees of confidentiality, privacy, and security. The sources of data may include individual doctors' records, billing information, vital statistics on births and deaths, health surveys, and data associated with biospecimens, among other sources.

The broad goal of registries is to amass data from potentially diverse sources to allow researchers to explore and evaluate alternative health outcomes in a systematic fashion. This goal is usually accomplished by gathering data from multiple sources and linking the data across sources, either with explicit identifiers designed for linking, or in a probabilistic fashion via the characteristics of the individuals to whom the data correspond. From the research perspective, the more data included, the better, both in terms of the number of cases and the details and the extent of the health information. The richer the database, the more likely it is that data analysts will be able to discover relationships that might affect or improve health care. On the other hand, many discussions about privacy protection focus on limiting the level of detail available in data to which others have access.

There is an ethical obligation to protect patient interests when collecting, sharing, and studying person-specific biomedical information.[1] Many people fear that information derived from their medical or biological records will be used against them in employment decisions, result in limitations to their access to health or life insurance, or cause social stigma.[2] These fears are not unfounded, and there have been various cases in which it was found that an individual's genetic characteristics or clinical manifestations

were used in a manner inconsistent with an individual's expectations of privacy and fair use.[3] If individuals are afraid that their health-related information may be associated with them or used against them, they may be less likely to seek treatment in a clinical context or participate in research studies.[4]

A tension exists between the broad goals of registries and regulations protecting individually identifiable information. Approaches and formal methodologies that help mediate this tension are the principal technical focus of this chapter. To understand the extent to which these tools can assist data linkages involving registry data, one needs to understand the risks of identification in different types of data.

There is a large body of Federal law relating to privacy. A recent comprehensive review of privacy law and its effects on biomedical research identified no fewer than 15 separate Federal laws pertaining to health information privacy.[5] There are also special Federal laws governing health information related to substance abuse.[6] A full review of all laws related to privacy, confidentiality, and security of health information also would consider separate State privacy protections, as well as State laws pertaining to the confidentiality of data. Nevertheless, the legal aspects of this chapter focus only on the Federal regulations commonly referred to as the HIPAA Privacy Rule.

2.2. What Do Privacy, Disclosure, and Confidentiality Mean?

Privacy is a term whose definition varies with context.[7] In the HIPAA Privacy Rule, the term applies to protected health information (PHI); specifically, to permitted uses and disclosures of individually identifiable health information. The Privacy Rule addresses to whom the custodian of PHI, a *covered entity*, may transmit the information and under what conditions. It establishes three basic concepts of health information: identifiable data; data that lack certain direct identifiers, otherwise known as a *limited dataset*; and de-identified data. Registries commonly acquire identifiable data and may create the last two categories of data. Along this spectrum of data, the HIPAA Privacy Rule applies different legal standards and protections.[5] Not all registries contain PHI; Chapter 7 provides more information on how PHI is defined under HIPAA. *Disclosure* has two different meanings: one is technical and the other is a HIPAA Privacy Rule definition.

2.2.1. Technical Definition

Technically, disclosure relates to the attribution of information to the source of the data, regardless of whether the data source is an individual or an organization. There are basically three types of disclosure of data that possess the capacity to make the identity of particular individuals known: *identity disclosure, attribute disclosure*, and *inferential disclosure*.

Identity disclosure occurs when the data source becomes known from the data release itself.[8,9]

Attribute disclosure occurs when the released data make it possible to infer the characteristics of an individual data source more accurately than would have otherwise been possible.[8,9] The usual way to achieve attribute disclosure is through identity disclosure. First, one identifies an individual through some combination of variables and then learns about the values of additional variables included in the released data. Attribute disclosure may occur, however, without identity disclosure, such as when all people from a population subgroup share a characteristic and this quantity becomes known for any individual in the subgroup.

Inferential disclosure relates to the probability of identifying a particular attribute of a data source. Because almost any data release can be expected to increase the likelihood of an attribute being associated with a data source, the only way to guarantee protection is to release no data at all. It is for this reason that researchers use certain methods not to prevent disclosure, but to limit or control the nature of the disclosure. These methods are known as disclosure limitation methods or statistical disclosure control.[10]

2.2.2. HIPAA Privacy Rule Definitions

Disclosure according to the HIPAA Privacy Rule means the release, transfer, provision of, access to, or divulging in any other manner of information outside of the entity holding the information.[11] *Confidentiality* broadly refers to a quality or condition of protection accorded to statistical information as an obligation not to permit the transfer of that information to an unauthorized party.[5] Confidentiality can be owed to both individuals and health care organizations. A different notion of confidentiality, arising from the special relationship between a clinician and patient, refers to the ethical, legal, and professional obligation of those who receive information in the context of a clinical relationship to respect the privacy interests of their patients. Most often the term is used in the former sense and not in the latter, but these two meanings inevitably overlap in a discussion of health information as data. The methods for disclosure limitation described here have been developed largely in the context of confidentiality protection, as defined by laws, regulations, and especially by the practices of statistical agencies.

2.3. Linking Records and Probabilistic Matching

Computer-assisted record linkage goes back to the 1950s, and was put on a firm statistical foundation by Fellegi and Sunter.[12] Most common techniques for record linkage either rely on the existence of unique identifiers or utilize a structure similar to the one Fellegi and Sunter described with the incorporation of formal statistical modeling and methods, as well as new and efficient computational tools.[13,14] The simplest way to match records from separate databases is to use a so-called "deterministic" method of linking the databases employing unique identifiers contained in each record. In the United States, these identifiers might be names or Social Security Numbers; however, these particular identifiers may not in fact be unique. As a result, some form of probabilistic approach is typically used to match the records. Thus, there is little actual difference between methods using deterministic vs. probabilistic linkage, except for the explicit representation of uncertainty in the matching process in the latter.

The now-standard approach to record linkage is built on five key components for identifying matching pairs of records across two databases:[13]

1. Represent every pair of records using a vector of features (variables) that describe similarity between individual record fields. Features can be Boolean, discrete, or continuous.

2. Place feature vectors for record pairs into three classes: matches (M), nonmatches (U), and possible matches (P). These correspond to "equivalent," "nonequivalent," and "possibly equivalent" (e.g., requiring human review) record pairs, respectively.

3. Perform record-pair classification by calculating the ratio $(P(\gamma \mid M)) / (P(\gamma \mid U))$ for each candidate record pair, where γ is a feature vector for the pair and $P(\gamma \mid M)$ and $P(\gamma \mid U)$ are the probabilities of observing that feature vector for a matched and nonmatched pair, respectively. Two thresholds based on desired error levels—$T\mu$ and $T\lambda$—optimally separate the ratio values for equivalent, possibly equivalent, and nonequivalent record pairs.

4. When no training data in the form of duplicate and nonduplicate record pairs are available, matching can be unsupervised; that is, conditional probabilities for feature values are estimated using observed frequencies in the records to be linked.

5. Most record pairs are clearly nonmatches, so one need not consider them for matching. This situation is managed by "blocking," or partitioning the databases, for example, based on geography or some other variable in both databases, so that only records in comparable blocks are compared. Such a strategy significantly improves efficiency.

The first four components lay the groundwork for accuracy of record-pair matching using statistical or machine learning prediction models, such as logistic regression. The fewer identifiers used in steps 1 and 2, the poorer the match is likely to be. Accuracy is well known to be high when there is a 1–1 match between records in the two databases, and accuracy deteriorates as the overlap between the files decreases and the measurement error in the feature values consequently increases.

The fifth component provides for efficiently processing large databases, but to the extent that blocking is approximate and possibly inaccurate, its use decreases the accuracy of record-pair matching. The less accurate the matching, the more *error* (i.e., records not matched or matched inappropriately) there will be in the merged registry files. This error will impede quality analyses and findings from the resulting data.[15,16]

This standard approach has problems when there are lists or files with little overlap, when there are undetected duplications within files, and when one needs to link three or more lists. In the latter case, one essentially matches all lists in pairs, and then resolves discrepancies. Unfortunately, there is no single agreed-upon way to do this. Record linkage methodology has been widely used by statistical agencies, especially in the U.S. Census Bureau. The methodology has been combined with disclosure limitation techniques such as the addition of "noise" to variables in order to produce public use files that the agencies believe cannot be linked back to the original databases used for the record linkage. Another technique involves protecting individual databases by stripping out identifiers and then attempting record linkage. This procedure has two disadvantages: first, the quality of matches is likely to decrease markedly; and second, the resulting merged records will still need to be protected by some form of disclosure limitation. Therefore, as long as there are no legal restrictions against the use of identifiers for record linkage purposes, it is preferable to use detailed identifiers to the extent possible and to remove them following the matching procedure.

Currently there are no special features of registry data known to enhance or inhibit matching. Registry data may be easier targets for re-identification because the specifics of diseases or conditions help to define the registries. In the United States, efforts are often made to match records using Social Security Numbers. There are large numbers of entry errors for these numbers in many databases, and there are problems associated with multiple people using one number and some people using multiple numbers.[17] Lyons et al. describe a very large-scale matching exercise in the United Kingdom linking multiple health care and social services datasets using National Health Service numbers and various alternative sets of matching variables in the spirit of the record linkage methods described above. They report achieving accurate matching at rates of only about 95 percent.[18]

2.4. Procedural Issues in Linking Datasets

It is important to understand that neither *data* nor *link* can be unambiguously defined. For instance, a dataset may be altered by the application of tools for statistical disclosure limitation, in which case it is no longer the same dataset. Linkage need not mean, as it is customarily construed, "bringing the two (or more) datasets together on a single computer." Many analyses of interest can be performed using technologies that do not require literal integration of the datasets. Even the relationship between datasets can vary. Two datasets can hold the same attributes for different individuals (*horizontal partitioning*), different attributes for the same individuals (*vertical partitioning*), or a complex combination of the two.

The process of linking horizontally partitioned datasets engenders little incremental risk of reidentification. There is, in almost all cases, no more information about a record on the combined dataset than was present in the individual dataset containing it. Moreover, any analysis requiring only data summaries (i.e., in technical terms, sufficient statistics) that are additive across the datasets can be performed using tools based on the computer science concept of secure summation.[19] Examples of analyses for which this approach works include creation of contingency tables, linear regression, and some forms of maximum likelihood estimation.

Only in a few cases have comparable techniques for vertically partitioned data been well enough understood to be employed in practice.[20] Instead, it is usually necessary to actually link individual subjects' records that are contained in two or more datasets. This process is inherently and unavoidably risky because the combined dataset contains more information about each subject than either of the components.

Discussed below is a preferred approach that is complex, but that attenuates or can even obviate other problems. Suppose that each of the two datasets to be linked contains the same unique identifiers (for individuals, an example is Social Security Numbers) in all of the records. In this case, there exist techniques based on cryptography (homomorphic encryption[21] and hash functions) that enable secure determination of which individuals are common to both datasets and assignment of unique but uninformative identifiers to the shared records. Each dataset can then be purged of individual identifiers and altered to further limit reidentification, following which error-free and riskfree linkage can be performed.

Such techniques are computationally very complex, and may need to involve trusted third parties that do not have access to information in either dataset other than the common identifier. Therefore, in many cases the database custodian may prefer to remove identifiers and carry out statistical disclosure limitation prior to linkage. It is important to understand that this latter approach compromises, perhaps irrevocably, the linkage process, and may introduce errors into the linked dataset that later— perhaps dramatically— alter the results of statistical analyses.

Many techniques for record linkage depend at some level on the presence of sets of attributes in both databases that are unique to individuals but do not lead to re-identification—a combination that may be difficult to find. For instance, the combination of date of birth, gender, and ZIP Code of residence might be present in both databases. It is estimated that this combination of attributes uniquely characterizes a significant portion of the U.S. population—somewhere between 65 and 87 percent, or even higher for certain subpopulations—so reidentification would only require access to a suitable external database.[22,23] Other techniques such as the Fellegi-Sunter record linkage methods described above are more

probabilistic in nature. They can be effective, but as noted, they also introduce data quality effects that cannot readily be characterized.

No matter how linkage is performed, a number of other issues should be addressed. For instance, comparable attributes should be expressed in the same units of measure in both datasets (e.g., English or metric values for weight). Also, conflicting values of attributes for each individual common to both databases need reconciliation. Another issue involves the management of records that appear in only one database; the most common decision is to drop them. Data quality provides another example; it is one of the least understood statistical problems and has multiple manifestations.[24] Even assuming some limited capability to characterize data quality, the relationship between the quality of the linked dataset and the quality of each component should be considered. The linkage itself can produce quality degradation. The best way to address these issues is not clear, and intuition can be faulty. For example, there is reason to believe that the quality of a linked dataset is strictly less than that of either component, and not, as might be supposed, somewhere between the two.

Finally, it is important to understand that there exist endemic risks to data linkage. Anyone with access to one of the original datasets and the linked dataset may learn, even if imperfectly, the values of attributes in the other. It may not be possible to determine what knowledge the linkage will create without actually executing the linkage. For these reasons, strong consideration should be given to forms of data protection such as licensing and restricted access in research data centers, where both analyses and results can be controlled.

3. Legal Aspects of Data Linkage Projects

3.1. Risks of Identification

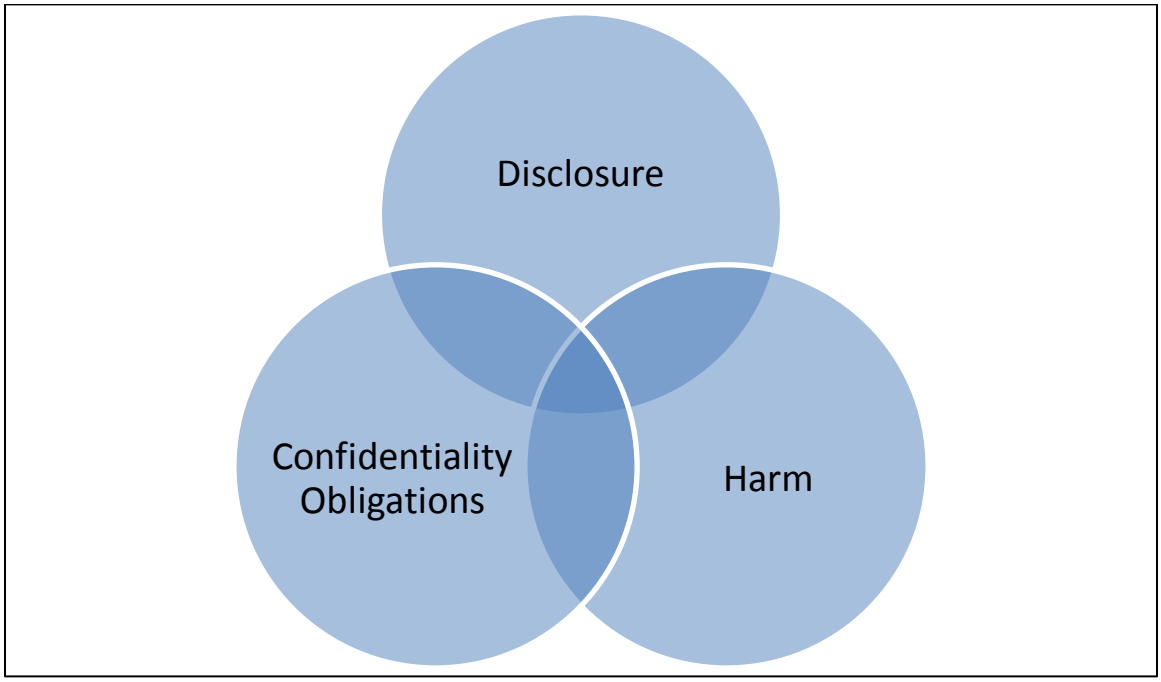
The HIPAA Privacy Rule describes two methods for de-identifying health information.[25] One method requires the removal of certain data elements. The other method requires a qualified statistician to certify that the potential for identifying an individual from the data elements is negligible. (See Chapter 7 for more information.) The data removal process alone may not be sufficient. Residual data especially vulnerable to disclosure threats include (1) geographic detail, (2) longitudinal information, and (3) extreme values (e.g., income). Population health data are clearly more vulnerable than sample data, and variables that are available in other accessible databases pose special risks.

Statistical organizations such as the National Center for Health Statistics have traditionally focused on the issue of identity disclosure and thus refuse to report information in which individuals or institutions can be identified. This situation occurs, for example, when a data source is unique in the population for the characteristics under study, and is directly identifiable in the database to be released. But such uniqueness and subsequent identity disclosure may not reveal any information other than the association of the source with the data collected in the study. In this sense, identity disclosure may only be a technical violation of a promise of confidentiality. Thus, uniqueness only raises the issue of possible confidentiality problems resulting from identification. A separate issue is whether the release of information is one that is permitted by the HIPAA Privacy Rule or is authorized by the data source.

The foregoing discussion implicitly introduces the notion of "harm," which is not the same as a breach of confidentiality. For example, it is possible for a pledge of confidentiality to be technically violated, but produce no harm to the data source because the information is "generally known" to the public. In this

case, some would argue that additional data protection is not required. Conversely, if one attempts to match records from one file to another file which is subject to a pledge of confidentiality, and an "incorrect" match is made, there is no breach of confidentiality, but there is the possibility of harm if the match is assumed to be correct. Furthermore, information on individuals or organizations in a release of sample statistical data may well increase the information about characteristics of individuals or organizations not in the sample. This information may produce an inferential disclosure for such individuals or organizations and cause them harm, even though there was no confidentiality obligation. Figure 10 depicts the overlapping relationships among confidentiality, disclosure, and harm.

Figure 10. Relationships among Confidentiality, Disclosure, and Harm



Some people believe that the way to ensure confidentiality and prevent identity disclosure is to arrange for individuals to participate in a study anonymously. In many circumstances, such a belief is misguided, because there is a key distinction between collecting information anonymously and ensuring that personal identifiers are not inappropriately made available. Moreover, clinical health care data are simply not collected anonymously. Not only do patient records come with multiple identifiers crucial to ensuring patient safety for clinical care, but they also contain other information that may allow the identification of patients even if direct identifiers are stripped from the records.

Moreover, health- or medical-related data may also come from sample surveys in which the participants have been promised that their data will not be released in ways that would allow them to be individually identified. Disclosure of such data can produce substantial harm to the personal reputations or financial interests of the participants, their families, and others with whom they have personal relationships. For example, in the pilot surveys for the National Household Seroprevalence Survey, the National Center for Health Statistics moved to make responses during the data collection phase of the study anonymous because of the harm that could potentially result from information that an individual had an HIV infection or engaged in high-risk behavior. But such efforts still could not guarantee that one could not identify a

participant in the survey database. This example also raises an interesting question about the confidentiality of registry data after an individual's death, in part because of the potential for harm to others. The health information of decedents is subject to the HIPAA Privacy Rule, and several statistical agencies explicitly treat the identification of a deceased individual as a violation of their confidentiality obligations.

3.1.1. Examples of Patient Re-Identification

For years, the confidentiality of health information has been protected through a process of "deidentification." This protection entails the removal of person-specific features such as names, residential street addresses, phone numbers, and Social Security Numbers. However, as discussed above, de-identification does not guarantee that individuals may not be identified from the resulting data. On multiple occasions, it has been shown that de-identified health information can be "reidentified" to a particular patient without hacking or breaking into a private health information system. For instance, in the mid-1990s Latanya Sweeney, then a graduate student at the Massachusetts Institute of Technology, showed that de-identified hospital discharge records, which were made publicly available at the State level, could be linked to identifiable public records in the form of voter registration lists. Her demonstration received notoriety because it led to the re-identification of the medical status of the then-governor in the Commonwealth of Massachusetts.[26] This result was achieved by linking the data resources on their common fields of patient's date of birth, gender, and ZIP Code. As noted earlier, this combination identifies unique individuals in the United States at a rate estimated at somewhere between 65 and 87 percent or even higher in certain subpopulations.

3.1.2. High-Risk Identifiers

One response to the Sweeney demonstration was the HIPAA Privacy Rule method for de-identification by removal of data elements. This process requires the removal of explicit identifiers such as names, dates, geocodes (for populations of less than 20,000 inhabitants), and other data elements that, in combination, could be used to ascertain an individual's identity. In all, the de-identification standard enumerates 18 features that should be removed from patient information prior to data sharing. (See Chapter 7.)[27] Nonetheless, even the removal of these data elements may fail to prevent re- identification. In many instances, there are residual features that can lead to identification. The extent to which residual features can be used for re-identification depends on the availability of relevant data fields. Thus, one can roughly partition identifiers into "high" and relatively "low" risk features. The high-risk features are the sort that are documented in multiple environments and are publicly available. These are features that could be exploited by any recipient of such records. For instance, patient demographics are high-risk identifiers. Even de-identified health information permitted under the HIPAA Privacy Rule may leave certain individuals in a unique status, and thus at high risk for identification through public data resources containing similar features, such as public records containing birth, death, marriage, voter registration, and property assessment information.

3.1.3. Relatively Low-Risk Identifiers

In contrast, lower-risk data elements are those that do not appear in public records and are less available. For instance, clinical features, such as an individual's diagnosis and treatments, are relatively static because they are often mapped to standard codes for billing purposes. These features might appear in de-identified information, such as hospital discharge databases, as well as in identified resources such as electronic medical records. While combinations of diagnostic and treatment codes might uniquely

describe an individual patient in a population, the identifiable records are available to a much smaller group than the general public. Moreover, these select individuals, such as the clinicians and business associates of the custodial organization for the records, are ordinarily considered to be trustworthy, because they owe independent ethical, professional, and legal duties of confidentiality to the patients.

3.1.4. Special Issues with Linkages to Biospecimens

Health care is increasingly moving towards evidence-based and personalized systems. In support of this trend, there is a growing focus on associations between clinical and biological phenomena. In particular, the decreasing cost of genome sequencing technology has facilitated a rapid growth in the volume of biospecimens and derived DNA sequence data. As much of this research is sponsored through Federal funding, it is subject to Federal data sharing requirements. However, biospecimens, and DNA in particular, are inherently unique and there are a number of routes by which DNA information can be identified to an individual.[28] For instance, there are over a million single nucleotide polymorphisms (SNPs) in the human genome; these little snippets of DNA are often used to make genetic correlations with clinical conditions. Yet it is estimated that fewer than one hundred SNPs can uniquely represent an individual.[29] Thus, if de-identified biological information is tied to sensitive clinical information, it may provide a match to the identified biological information—as, for example, in a forensic setting.[30]

Biospecimens and information derived from them are of particular concern because they can convey knowledge not only about the individual from whom they are derived, but also about other related individuals. For instance, it is possible to derive estimates about the DNA sequence of relatives.[31] If the genetic information is predictive or diagnostic, it can adversely affect the ability of family members to obtain insurance and employment, or it may cause social stigmatization.[32,33,34] The Genetic Information Nondiscrimination Act of 2008 (GINA) prohibits health insurers from using genetic information about individuals or their family members, whether collected intentionally or incidentally, in determining eligibility and coverage, or in underwriting and premium setting. Insurers may, in collaboration with external research entities, request that policyholders undergo genetic testing, but a refusal to do so cannot be permitted to affect the premium or result in medical underwriting.[35]

4. Risk Mitigation for Data Linkage Projects

4.1. Methodology for Mitigating the Risk of Re-Identification

The disclosure limitation methods briefly described in this section are designed to protect against identification of individuals in statistical databases, and are among the techniques that data linkage projects involving registries are most likely to use. One problem these methods do not address is the simultaneous protection of individual and institutional data sources. The discussion here also relates to the problems addressed by secure computation methodologies, which are explored in the next section.

4.1.1. Basic Methodology for Statistical Disclosure Limitation

Duncan[36] categorizes the methodologies used for disclosure limitation in terms of disclosure limiting masks, i.e., transformations of the data where there is a specific functional relationship (possibly stochastic) between the masked values and the original data. The basic idea of masking involves data transformations. The goal is to transform an n x p data matrix Z through pre- and postmultiplication and the possible addition of noise, such as depicted in Equation (1):

$$Z \rightarrow AZB+C \quad (1)$$

where *A* is a matrix that operates on cases, *B* is a matrix that operates on variables, and *C* is a matrix that adds perturbations or noise to the original information. Matrix masking includes a wide variety of standard approaches to disclosure limitation:

- Adding noise,
- Releasing a subset of observations (deleting rows from *Z*),
- Cell suppression for cross-classifications,
- Including simulated data (adding rows to *Z*),
- Releasing a subset of variables (deleting columns from *Z*), and
- Switching selected column values for pairs of rows (data swapping).

This list also omits some methods, such as microaggregation and doubly random swapping, but it provides a general idea of the types of techniques being developed and applied in a variety of contexts, including medicine and public health. The possibilities of both identity and attribute disclosure remain even when a mask is applied to a dataset, although the risks may be substantially diminished.

Duncan suggests that we can categorize most disclosure-limiting masks as suppressions (e.g., cell suppression), recodings (e.g., collapsing rows or columns, or swapping), or samplings (e.g., releasing subsets), although he also allows for simulations as discussed below. Further, some masking methods alter the data in systematic ways (e.g., through aggregation or through cell suppression), whereas others do it through random perturbations, often subject to constraints for aggregates. Examples of perturbation methods are controlled random rounding, data swapping, and the postrandomization method (PRAM) of Gouweleeuw,[37] which has been generalized by Duncan and others. One way to think about random perturbation methods is as restricted simulation tools. This characterization connects them to other types of simulation approaches.

Various authors pursue simulation strategies and present general approaches to "simulating" from a constrained version of the cumulative, empirical distribution function of the data. In 1993, Rubin asserted that the risk of identity disclosure could be eliminated by the use of synthetic data (in his case using Bayesian methodology and multiple imputation techniques) because there is no direct function link between the original data and the released data.[38] Said another way, the data remain confidential because simulated individuals have replaced all of the real ones. Raghunathan, Reiter, and Rubin[39] provide details on the implementation of this approach. Abowd and Woodcock (for their chapter in Doyle et al., 2001)[40] describe a detailed application of multiple imputation and related simulation technology for a longitudinally linked individual and work history dataset. With both simulation and multiple-imputation methodology, however, it is still possible that the data values of some simulated individuals remain virtually identical to those in the original sample, or at least close enough that the possibility of both identity and attribute disclosure remain. As a result, checks should be made for the possibility of unacceptable disclosure risk.

Another important feature of the statistical simulation approach is that information on the variability of the dataset is directly accessible to the user. For example, in the Fienberg, Makov, and Steele[41] approach for categorical data, the data user can begin with the reported table and information about the margins that are held fixed, and then run the Diaconis-Sturmfels Monte Carlo Markov chain algorithm to regenerate the full distribution of all possible tables with those margins. This technique allows the user to make inferences about the added variability in a modeling context that is similar to the approach to inference in

Gouweleeuw et al.[37] Similarly, Raghunathan and colleagues proposed the use of multiple imputations to directly measure the variability associated with the posterior distribution of the quantities of interest.[39] As a consequence, Rubin showed that simulation and perturbation methods represent a major improvement in access to data over cell suppression and data swapping without sacrificing confidentiality. These methods also conform to the statistical principle allowing the user of released data to apply standard statistical operations without being misled.

There has been considerable research on disclosure limitation methods for tabular data, especially in the form of multiway tables of counts (contingency tables). The most popular methods include a process known as cell suppression, which systematically deletes the values in selected cells in the table and collapses categories. This process is a form of aggregation. While cell suppression methods have been very popular among the U.S. Government statistical agencies, and are useful for tables with nonnegative entries rather than simple counts, they also have major drawbacks. First, good algorithms do not yet exist for the methodology when it is associated with high-dimensional tables. More importantly, the methodology systematically distorts the information about the cells in the table for users, and, as a consequence, makes it difficult for secondary users to draw correct statistical inferences about the relationships among the variables in the table. For further discussion of cell suppression and extensive references, see the various chapters in Doyle et al.,[40] notably the one by Duncan and his collaborators.

A special example of collapsing categories involves summing over variables to produce marginal tables. Instead of reporting the full multiway contingency table, one or more collapsed versions of it might be reported. The release of multiple sets of marginal totals has the virtue of allowing statistical inferences about the relationships among the variables in the original table using log-linear model methods (e.g., see Yvonne, Bishop, Fienberg, and Holland).[42] With multiple collapsed versions, statistical theory makes it clear that one may have highly accurate information about the actual cell entries in the original table. As a result, the possibility of disclosures still requires investigation. In part to address this problem, a number of researchers have recently worked on the problem of determining upper and lower bounds for the cells of a multi-way table given a set of margins; however, other measures of risk may clearly be of interest. The problem of computing bounds is in one sense an old one, at least for two-way tables, but it is also deeply linked to recent mathematical developments in statistics and has generated a flurry of new research.[43,44]

4.1.2. The Risk-Utility Tradeoff

Common to virtually all the methodologies discussed in the preceding section is the notion of a risk-utility tradeoff, in which the risk of disclosure is balanced with the utility of the released data (e.g., see Duncan,[36] Fienberg,[45] and their chapter with others in Doyle et al.[40]). To keep this risk at a low level requires applying more extensive data masking, which limits the utility of what is released. Advocates for the use of simulated data often claim that this use eliminates the risk of disclosure, but still others dispute this claim.

4.1.3. Privacy-Preserving Data Mining Methodologies

With the advances in data mining and machine learning over the past two decades, there have been a large number of methods introduced under the banner of privacy-preserving computation. The methodologies vary, and many of them focus on standard tools such as the addition of noise or data swapping of one sort or another. But the claims of identity protection in this literature are often exaggerated or unverifiable. For

a discussion of some of these ideas and methods, see Fienberg and Slavkovic.[44] For two recent interesting examples explicitly set in the context of medical data, see Malin and Sweeney[46] and Boyens, Krishnan, and Padman.[47]

The common message of this literature is that privacy protection has costs measured in the lack of availability of research data. To increase the utility of released data for research, some measure of privacy protection, however small, needs to be sacrificed. It is nonetheless still possible to optimize utility, subject to predefined upper bounds on what is considered to be acceptable risk of identification. See a related discussion in Fienberg.[48]

4.1.4. Cryptographic Approaches to Privacy Protection

While the current risks of identification in modern databases are similar for statistical agencies and biomedical researchers, there are also new challenges: from contemporary information repositories that store social network data (e.g., cell phone, Twitter, and Facebook data), product preferences data (e.g., Amazon), Web search data, and other sources of information not previously archived in a digital format. A recent literature emanating from cryptography focuses on algorithmic aspects of this problem with an emphasis on automation and scalability of a process for conferring anonymity. Automation, in turn, presents a fundamentally different perspective on how privacy is defined and provides for both a formal definition of privacy and proofs for how it can be protected. By focusing on the properties of the algorithm for anonymity, it is possible to formally guarantee the degree of privacy protection and the quality of the outputs in advance of data collection and publication.

This new approach, known as differential privacy, limits the incremental information a data user might learn beyond that which is known before exposure to the released statistics. No matter what external information is available, the differential privacy approach guarantees that the same information is learned about an individual, whether or not information about the individual is present in the database. The papers by Dwork et al.[49,50] provide an entry point to this literature. Differential privacy, as these authors describe it, works primarily through the addition of specific forms of noise to all data elements and the summary information reported, but it does not address issues of sampling or access to individual-level microdata. While these methods are intriguing, their utility for data linkages with registry data remains an open issue.

4.1.5. Security Practices, Standards, and Technologies

In general, people adopt two different philosophical positions about how the confidentiality associated with individual-level data should be preserved: (1) by "restricted or limited information," that is, restrictions on the amount or format of the data released, and (2) by "restricted or limited access," that is, restrictions on the access to the information itself.

If registry data are a public health good, then restricted access is justifiable only in situations where the confidentiality of data in the possession of a researcher cannot be protected through some form of restriction on the information released. Restricted access is intended to allow use of unaltered data by imposing certain conditions on users, analyses, and results that limit disclosure risk. There are two primary forms of restricted access. The first is through licensing, whereby users are legally bound by certain conditions, such as agreeing not to use data for re-identification and to accept advance review of publications. The licensure approach allows users to transfer data to their sites and use the software of their choice. The second approach is exemplified by research data centers, discussed in more detail below, and remote analysis servers, which are conceptually similar to data centers: users, and sometimes

analyses, are evaluated in advance. The results are reviewed, and often limited, in order to limit risk of disclosure. The data remain at the holder's site and computers; the difference is whether access is in person at a data center or using a remote analysis center via the World Wide Web.

4.1.6. Registries as Data Enclaves

Many statistical agencies have built enclaves, often referred to as research data centers, where users can access and use data in a regulated environment. In such settings, the security of computer systems is controlled and managed by the agency providing the data. Such environments may maximize data security. For a more extensive discussion of the benefits of restricted access, see the chapter by Dunne in Doyle et al.[40]

These enclaves incur considerable costs associated with their establishment and upkeep. A further limitation is that the enclave may require the physical presence of the data user, which also increases the overall cost to researchers working with the data. Moreover, such environments often prevent users from executing specialized data analyses, which may require programming and other software development beyond the scope of traditional statistical software packages made available in the enclave.

The process for access to data in enclaves or restricted centers involves an examination of the research credentials of those wishing to do so. In addition, these centers control the physical access to confidential data files and they review the materials that data users wish to take from the centers and to publish. Researchers who are accustomed to reporting residual plots and other information that allows for a partial reconstruction of the original data, at least for some variables, will encounter difficulties, because restricted data centers typically do not allow users to remove such information.

4.1.7. Accountability

To limit the possibility of re-identification, data can be manipulated by the above techniques to mitigate risk. At the same time, it is important to ensure that researchers are accountable for the use of the datasets that are made available to them. Best practices in data security should be adopted with specific emphasis on authentication, authorization, access control, and auditing. In particular, each data recipient should be assigned a unique login identification (ID), or, if the data are made available online, access may be provided through a query response server. Prior to each session of data access, data custodians should authenticate the user's identity. Access to information should be controlled either in a role-based or information-based manner. Each user access and query to the data should be logged to enable auditing functions. If there is a breach in data protection, the data custodian can investigate the potential cause and make any required notifications.

4.1.8. Layered Restricted Access to Databases

In many countries, the traditional arrangement for data use involves restrictions on both information and access, with only highly aggregated data and summary statistics released for public use.

One potential strategy for privacy protection for the linkage of registries to other confidential data is a form of layered restrictions that combines two approaches with differing levels of access at different levels of detail in the data. The registry might function as an enclave, similar to those described above, and in addition, public access might be limited to only aggregate data. Between these two extremes there might be several layers of restricted access. An example is licensing that includes privacy protection, requiring greater protection as the potential for disclosure risk increases.

Such a layered approach might require a broader interpretation of the HIPAA Privacy Rule restrictions for certain kinds of medical records[5] or different forms of releases for patient records. The HIPAA Privacy Rule's detailed approach to releasing data can be shown to protect individual data only partially, and at the same time, to unnecessarily restrict access to medical record data for research purposes. As a result, there is a need to develop a clearer sense of how health information subject to the HIPAA Privacy Rule might be linked with registry data and subsequently protected. Such clarifications could allow for more complete research data while offering protection against the risks of identity disclosure to individuals and health care providers.

5. Summary

This chapter describes technical and current legal considerations for researchers interested in creating data linkage projects involving registry data. The discussion of the HIPAA Privacy Rule provides a basis for understanding the conditions under which the use and disclosure of protected health information (PHI) is permitted for research and other purposes relevant to registries. These conditions determine whether and how the linkage of certain datasets may be legally feasible. In addition, the chapter presents typical methods for record linkage that are likely to form the basis for the construction of data linkage projects. It also discusses both the hazards for re-identification created by data linkage projects, and the statistical methods used to minimize the risk of re-identification. Two topics not covered in this chapter are: (1) considerations about linking data from public and private sectors, where different, perhaps conflicting, ethical and legal restrictions may apply, and (2) the risks involved in identifying the health care providers that collect and provide data.

Dataset linkage entails the risks of loss of reliable confidential data management and of identification or re-identification of individuals and institutions. Recognized and developing statistical methods and secure computation may limit these risks and allow the public the health benefits that registries linked to other datasets have the potential to contribute.

6. Legal and Technical Planning Questions

The questions in Tables 22 and 23 are intended to assist in the planning of data linkage projects that involve using registry data plus other files. Registry operators should use the answers to these questions to assemble necessary information and other resources to guide planning for their data linkage projects. Like the preceding discussion, this section considers regulatory and technical questions.

The assumptions listed below in Table 22 apply to the regulatory questions that follow. Their application to the proposed data linkage project should be confirmed or determined.

- The HIPAA Privacy Rule applies to the initial data sources.
- Other laws may restrict access or use of the initial data sources.
- The Common Rule or FDA regulations may or may not apply to data linkage.
- The Common Rule or FDA regulations may or may not apply to the original datasets.

Different regulatory concerns arise depending on the answers to each category of the following questions. Consult as necessary with experienced health services, social science, or statistician colleagues; and with regulatory personnel (e.g., the agency Privacy Officer) or legal counsel to clarify answers for specific data linkage projects.

Table 22. Legal Planning Questions

1. Purpose for data linkage	• Research? • Public health? • Quality improvement? • Required for postmarketing safety studies? • Determining effectiveness of a product or service? • Other purpose? • Combination of purposes?
2. Conditions under which data (plus or minus biospecimens) were originally collected	• Collected by law (e.g., regulatory purpose, public health purpose)? • For treatment, payment, or health care operations? • With documented consent from each individual to research participation and authorization for research use of protected health information? • With an IRB alteration or waiver of consent and authorization? • With permission of health care provider or plan? • With contractual conditions or limitations on future use or disclosure (release)? • What are the reasonable expectations, held by the original data sources and the data custodians, of privacy or confidentiality for future uses of the data?
3. Data	• Is sensitive information involved (e.g., about children, infectious disease, mental health conditions)? • Do the data contain direct identifiers? Indirect identifiers? • Is protected health information (PHI) involved? • Is a limited dataset (LDS), and thus a data use agreement (DUA), involved? • Are the data de-identified in accordance with the HIPAA Privacy Rule? • Do the data contain a code to identifiers? • Who holds the key to the code? • Is a neutral third party (an honest broker) involved? • Does the code to identifiers conform to the re-identification standard in the HIPAA Privacy Rule? • Is re-identification needed prior to performing the data linkage? • After the data linkage, will the risk increase that the data may be identifiable? • What is the minimally acceptable cell size to avoid identifying individuals?
4. The person or institution holding the data for the linkage	• Is this person or institution a covered entity under the HIPAA Privacy Rule or the American Recovery and Reinvestment Act of 2009? • Not a covered entity?
5. The person or institution performing data linkage	• Is this person or institution a covered entity under the HIPAA Privacy Rule or the American Recovery and Reinvestment Act of 2009? • Not a covered entity?
6. Other laws or policies that may apply to data use or disclosure (release)	• Are governmental data involved? • Are NIH data sharing policies involved? • Does State law apply? Which State?
7. The terms and conditions that apply to data disclosure (release) and use under any agreement with the	• For individuals as the data source, do the consent and authorization documents contain limitations on data use— unless the data have been sufficiently de-identified?

original source of the data	• For data custodians as the data source, is there a data use agreement or other contract that applies to data use by any subsequent holder of the data?
8. Anticipated needs for data validation and verification	• Initially for the data linkage processes? • In the future?
9. Future needs for privacy protection of the data source or maintenance of data confidentiality	• What will happen to data resulting from the linkage once the analyses have been completed? How will the data be stored?
10. Anticipated future uses of the linked data	• Will the data resulting from the linkage be maintained for multiple analyses? For the same or different purposes? • Will the data resulting from the linkage be used for other linkages? • What permissions are necessary for, or restrictions apply to, planned future uses of the data? • Are there currently requirements for tracking uses and disclosures of the data?

Note: *HIPAA is Health Insurance Portability and Accountability Act. IRB=institutional review board. NIH=National Institutes of Health.*

Table 23. Technical Planning Questions

• Who is performing the linkage? Are the individuals performing the linkage permitted access to identifiers or restricted sets of identifiers? Are they neutral agents ("honest brokers") or the source of one of the datasets to be linked?
• How easy will it be to know whether a given person is in the registry? Are censuses riskier than surveys?
• Is there a common feature or pseudonym (sets of attributes in both databases that are unique to individuals but do not lead to re-identification) available across the datasets being linked?
• Is the registry a flat file or a relational database? The latter is more difficult to manage unless a primary key is applied.
• Is the registry relatively static or dynamic? The latter is harder to manage if data are being added over time, because the risk of identification increases.
• How many attributes are in the registry? The more attributes, the harder it will be to manage the risk of identification associated with the registry.
• How will conflicting values of attributes that are common to both databases be resolved? Comparable attributes (e.g., weight) should be converted to the same units of measurement in datasets that will be linked.
• Does the registry contain information that makes the risk identification intrinsic to the registry? Direct identifiers such as names and Social Security Numbers are problematic, as is fine-scale geography.
• Is there a sound data dictionary?
• How many external databases will be linked to the registry data? How readily available and costly is each external database?
• How will records that appear in only one database be managed?
• How will the accuracy of the linked dataset relate to the accuracy of its components? The accuracy is only as good as that of the least accurate component.

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Case Examples for Chapter 16

Case Example 33. Linking Registries at the International Level

Description	Psonet is an investigator-initiated, international scientific network of coordinated population-based registries; its aim is to monitor the long-term effectiveness and safety of systemic agents in the treatment of psoriasis.
Sponsor	Supported initially by a grant from the Italian Medicines Agency (AIFA); supported since 2011 by a grant from the European Academy of Dermato Venereology (EADV) and coordinated by the Centro Studi GISED.
Year Started	2005
Year Ended	Ongoing
No. of Sites	9 different registries across Europe and an Australasian registry
No. of Patients	27,800

Challenge

The number of options for systemic treatment of psoriasis has greatly increased in recent years. Because psoriasis is a chronic disease involving lifelong treatment, data on long-term effectiveness and safety are needed for both old and new treatments. Several European countries have established patient registries for surveillance of psoriasis treatments and outcomes. However, these registries tend to have small patient populations and little geographic diversity, limiting their strength as surveillance tools for rare or delayed adverse events.

Proposed Solution

Combining the results from nation-based registries would increase statistical power and may enable investigators to conduct analyses that would not be feasible at a single-country level. Psonet was established in 2005 as a network of European registries of psoriasis patients being treated with systemic agents. The goal of the network is to improve clinical knowledge of prognostic factors and patient outcomes, thus improving treatment of psoriasis patients. An International Coordinating Committee (ICC), including representatives of the national registries and some national pharmacovigilance centers, oversees the network activities, including data management, publications, and ethical or privacy issues. The ICC has appointed an International Safety Review Board, whose job is to review safety data, prepare periodic safety reports, and set up procedures for the prompt identification and investigation of unexpected adverse events. Informed consent for data sharing is obtained before patients are enrolled in participating registries.

When drafting the registry protocol, member registries agreed to a common set of variables and procedures to be included and implemented in the national registries. However, some registries were already active at that time, and harmonization is not perfect. Although inclusion criteria, major outcomes, and follow-up schedules are quite similar among registries, there are some differences. There are also differences in terms of software used, data coding, and data ownership arrangements. These

factors made sharing individual patient data complicated, and an alternate solution was identified: meta-analysis of summary measures from each registry. As summary measures (or effect measures) are calculated, the methods used to obtain them are decided in advance, including methods used to control for confounding and methods used to temporarily link exposures and events.

Results

Ten national and local registries at different stages of development are associated with the registry to date, contributing a total of about 27,800 patients. While the registry is too new to have published results, planned activities and analyses include comparative data on treatment strategies for psoriasis in Europe, rapid alerts on newly recognized unexpected events, regular reports on effectiveness and safety data, and analyses of risk factors for lack of response as a preliminary step to identifying relevant biomarkers.

Key Point

Data from multiple registries in different countries may be combined to provide larger patient populations for study of long-term outcomes and surveillance for rare or delayed adverse events. Meta-analysis of prospectively calculated summary measures can be a useful tool.

For More Information

Psonet: European Registry of Psoriasis. Available at www.psonet.eu. Accessed August 31, 2012.

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Case Example 34. Linking a Procedure-Based Registry with Claims Data to Study Long-Term Outcomes

Description	The CathPCI Registry measures the quality of care delivered to patients receiving diagnostic cardiac catheterizations and percutaneous coronary interventions (PCI) in both inpatient and outpatient settings. The primary outcomes evaluated by the registry include the quality of care delivered, outcome evaluation, comparative effectiveness, and postmarketing surveillance.
Sponsor	American College of Cardiology Foundation (ACCF) through the National Cardiovascular Data Registry (NCDR). Funded by participation dues from catheterization laboratories.
Year Started	1998
Year Ended	Ongoing
No. of Sites	1,450 catheterization laboratories
No. of Patients	12.7 million patient records; 4.5 million PCI procedures

Challenge

The registry sponsor was interested in studying long-term patient outcomes for diagnostic cardiac catheterizations and percutaneous coronary interventions (PCI), but longitudinal data are not collected as part of the registry. Rather than create an additional registry, it was determined that the most feasible option was linking the registry data with available third-party databases such as Medicare.

Before the linkage could occur, however, several legal questions needed to be addressed, including what identifiers could be used for the linkage and whether institutional review board (IRB) approval was necessary.

Proposed Solution

The registry developers explored potential issues relating to the use of protected health information (Federal HIPAA [Health Insurance Portability and Accountability Act] laws) to perform the linkage; the applicability of the Common Rule (protection of human subjects) to the linkage; and the contractual obligations of the individual legal agreement with each participating hospital with regard to patient privacy. The registry gathers existing data that are collected as part of routine health care activities. Informed consent is not required. Direct patient identifiers are collected in the registry, and the registry sponsor has business associate agreements in place with participating catheterization laboratories.

After additional consultation with legal counsel, the registry sponsor concluded that the linkage of data could occur under two conditions: (1) that the datasets used in the merging process must be in the form of a *limited data set* (see Chapter 7), and (2) that an IRB must evaluate such linkage. The resulting decision was based on two key factors: First, the registry participant agreement includes a data use agreement, which permits the registry sponsor to perform research on a limited data set but also requires that no attempt be made to identify the patient. Second, since there was uncertainty as to whether the proposed data linkage would meet the definition of research on human subjects, the registry sponsor chose to seek IRB approval, along with a waiver of informed consent.

Results

The registry data were linked with Medicare data, using probabilistic matching techniques to link the limited datasets. A research protocol describing the need for linkage, the linking techniques, and the research questions to be addressed was approved by an IRB. Researchers must reapply for IRB approval for any new research questions that they wish to study in the linked data.

Results of the linkage analyses were used to develop a new measure, “Readmission following PCI,” for the Centers for Medicare & Medicaid Services hospital inpatient quality pay-for-reporting program.

Key Point

There are many possible interpretations of the legal requirements for linking registry data with other data sources. The interpretation of legal requirements should include careful consideration of the unique aspects of the registry, its data, and its participants. In addition, clear documentation of the way the interpretation occurred and the reasoning behind it will help to educate others about such decisions and may allay anxieties among participating institutions.

For More Information
https://www.ncdr.com/webncdr/DefaultCathPCI.aspx

Case Example 35. Linking Registry Data to Examine Long-Term Survival

Description	The Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) is a population-based registry that collects data on children and young adults diagnosed with a malignant neoplasm or certain benign neoplasms, living within the Yorkshire and Humber Strategic Health Authority (SHA). The goals of the registry are (1) to serve as a data source for research at local, national, and international levels on the causes of cancer in children, teenagers, and young people, and (2) to evaluate the delivery of care provided by clinical and other health service professionals.
Sponsor	Primary funding is provided by the Candlelighters Trust, Leeds.
Year Started	1974
Year Ended	Ongoing
No. of Sites	18 National Health Service (NHS) Trusts
No. of Patients	7,728

Challenge

In 2002, approximately 1,500 children in the United Kingdom (UK) were diagnosed with cancer. Previous estimates of malignant bone tumors in children have been approximately 5 per million person-years in the UK. The registry collects data on individuals under age 30 years living within the Yorkshire and Humber Strategic Health Authority (SHA), and diagnosed with a malignant neoplasm or certain benign neoplasms by pediatric oncology and hematology clinics or teenage and young adult cancer clinics. Primary patient outcomes of the registry include length of survival, access to specialist care, late effects following cancer treatment, and hospital activity among long-term survivors. While bone cancer is ranked as the seventh most common malignancy in the UK, the relative rarity of this type of childhood cancer makes it difficult to gather sufficient data to evaluate incidence and survival trends over time.

Proposed Solution

The registry participated in a collaborative effort to combine its data with three other population-based registries—the Northern Region Young Persons' Malignant Disease Registry (NRYPMDR), the West Midlands Regional Children's Tumour Registry (WMRCTR), and the Manchester Children's Tumour Registry (MCTR). Together, the four population-based registries represented approximately 35 percent of the children in England.

Results

In a 20-year period from 1981 to 2002, 374 cases of malignant bone tumors were identified in children ages 0 to 14 years. The age-standardized incidence rate for all types of bone cancers (i.e., osteosarcoma, chondrosarcoma, Ewing sarcoma, and other) was reported to be 4.84 per million per year. For the two

most common types of bone cancer, osteosarcoma and Ewing sarcoma, the incidence rates were 2.63 cases per million person-years (95-percent confidence interval [CI] of 2.27–2.99) and 1.90 cases per million person year (95-percent CI of 1.58–2.21), respectively. While an improvement in survival was observed in patients with Ewing sarcoma, no survival improvement was detected in patients with osteosarcoma. The 5-year survival rate for children with all types of diagnoses observed in the study was an estimated 57.8 percent (95-percent CI 52.5 to 63).

Key Point

In the analysis of rare diseases, the number of cases and deaths included in the study determines the statistical power for examining survival trends and significant risk factors, and the precision in estimating the incidence rate or other parameters of disease. In cases where it is difficult to obtain a large enough sample size within a single study, considerations should be given to combining registry data collected among similar patient populations.

For More Information

Eyre R, Feltbower RG, Mubwandarikwa E. et al. Incidence and survival of childhood bone tumours in Northern England and the West Midlands, 1981. Br J Cancer. 2002;2009(s100):188–93.

Case Example 36. Linking Longitudinal Registry Data to Medicaid Analytical Extract (MAX) Files

Description	The Cystic Fibrosis Foundation (CFF) Patient Registry is a rare disease registry that collects data from clinical visits, hospitalizations, and care episodes to track national trends in morbidity and mortality, assess the effectiveness of treatments, and to drive quality improvement in patients with cystic fibrosis (CF).
Sponsor	Cystic Fibrosis Foundation
Year Started	1986
Year Ended	Ongoing
No. of Sites	110 CFF-accredited care centers in the United States
No. of Patients	More than 26,000

Challenge

Clinical services and health information generated outside of clinic visits and hospitalizations at accredited care centers may or may not be captured in the CFF Patient Registry. Therefore, administrative claims data such as Medicaid Analytical Extract (MAX), with comprehensive information on reimbursed health services, are necessary to completely evaluate drug exposure for epidemiological studies. To protect patient information, the CFF Patient Registry only collects the last four digits of the social security number (SSN), gender, and date of birth as direct patient identifiers. Since these identifiers are largely non-unique, linkage of the registry data to other data sources presents a challenge.

Proposed Solution

A deterministic patient matching algorithm, or linkage rule, between the CFF Patient Registry and MAX data using non-unique patient identifiers was developed to link the two data sources. MAX patients (with at least two in- or outpatient claims with diagnosis for CF) and CFF registry patients born between January 1, 1981 and December 31, 2006 were included. We examined the following variables for linking plausibility: date of birth, last four digits of SSN, zip code, gender, date of sweat test, date of gene testing, and date of hospital admission. Specifically, we determined the percentage of unique records for each selected variable or combination of variables in the MAX dataset and the registry dataset. Only variable combinations with a 99% level of uniqueness (99% of unique records) were considered for the deterministic rule definitions. We then examined the linkage performance of each rule and the validation parameters (i.e., sensitivity, specificity, and positive predictive value [PPV]) of these rules were compared against the selected gold standard (defined as the rule with the highest linkage performance).

Results

We assessed 14,515 and 15,446 patient records in MAX and CF registry datasets, respectively. A total of nine linkage rules were established. The linkage rule including gender, date of birth, and SSN had the highest performance with 32.04% successfully linked records and was considered the gold standard. Linkage rule performance ranged from 1.4% (95% CI: 1.2 – 1.6) to 32.0% (95% CI: 31.3 – 32.8). As expected, rules with lower linkage performance had fewer or no matching records. Compared to the selected gold standard, the sensitivity of the other linkage rules ranged from 4.3% (95% CI: 3.8 – 4.9) to 73.3% (95% CI: 72.0 – 74.6); the specificity ranged from 88.2% (95% CI: 87.6 – 88.9) to 99.9% (95% CI: 99.8 – 99.9); and the PPV ranged from 68.2% (95% CI: 62.6 – 73.4) to 99.0% (95% CI: 96.5 – 99.8).

Key Point

The defined linkage rules exhibited varying operational characteristics of sensitivity, specificity, and PPV. Relying on multiple linkage rules may be necessary to optimize linkage performance when enhancing registry data with administrative claims data.

Chapter 17. Managing Patient Identity across Data Sources

1. Introduction

Electronic health care data are increasingly being generated and linked across multiple systems, including electronic health records (EHRs), patient registries, and claims databases. In general, every system assigns its own identifier to each patient whose data they maintain. This makes it difficult to track patients across multiple systems and identify duplicate patients when different systems are linked. Efforts to address this challenge are complicated by the need to protect patient privacy and security.

Patient identity management (PIM) has been defined as the "ability to ascertain a distinct, unique identity for an individual (a patient), as expressed by an identifier that is unique within the scope of the exchange network, given characteristics about that individual such as his or her name, date of birth, gender [etc.]."[1] For the purposes of this chapter, the scope of this definition will be expanded to refer to PIM as the process of accurately and appropriately identifying, tracking, managing, and linking individual patients and their digitized health care information, often within and across multiple electronic systems.[2,iv] There is an increased need for PIM strategies in the realm of health care data, and the primary reason for this is the continued rise in the quantity and linkage of electronic health care data.

The quantity of electronic health care data continues to grow. EHRs are increasingly being used to generate electronic health care data – about 50% of office-based physicians in the U.S. now use some form of EHR.[3] This number is likely to increase significantly in response to the EHR incentive programs enacted by the Centers for Medicare and Medicaid Services (CMS), which "provide a financial incentive for the "meaningful use" of certified EHR technology to achieve health and efficiency goals."[4] In addition to office-based EHRs, electronic health care data may be created by hospital EHRs, billing systems, insurance claims systems, pharmacy record systems, medical devices, and even by patients themselves via electronic patient health record systems. Large amounts of electronic health care data are also being generated from clinical research. Patient registries, for example, often use electronic data capture tools to collect and manage their data.

This increase in the quantity of electronic health care and research data creates new opportunities and need for data linkage. Pharmaceutical companies conducting clinical trials on specific genetic markers are seeking ways to more easily identify and recruit potential patients. EHRs and patient registries are interfacing with each other to minimize the burden of data entry on participating centers and practices (see Chapter 15). Data from patient registries and other electronic sources are being pooled together to form larger, more statistically powerful datasets for research and analysis (see Chapters 16 and 18 and Case Examples 39 and 40).

As more electronic health care data are generated and linked with each other, PIM has become crucial in order to (1) enable health record document consumers to obtain trusted views of their patient subjects, (2) facilitate data linkage projects, (3) abide by the current regulations concerning patient information-related

[iv] A related idea is the concept of patient identity integrity, which is defined as "the accuracy and completeness of data attached to or associated with an individual patient." Efficient patient identity management leads to high patient identity integrity. See HIMSS Patient Identity Integrity Work Group. Patient Identity Integrity. 2009. Available at: http://www.himss.org/content/files/PrivacySecurity/PIIWhitePaper.pdf. Accessed June 28, 2012

transparency, privacy, disclosure, handling, and documentation,[5] and (4) make the most efficient use of limited health care resources by reducing redundant data collection. To address this growing need, a number of standards development organizations are involved in the development of PIM strategies and standards. Several major organizations currently include: Integrating the Healthcare Enterprise (IHE); Health Level Seven International (HL7); and The Regenstrief Institute, Inc. See Appendix C for a more complete list.

2. Patient Identity Management Strategies

The challenge of patient identity management is not a new one, and has existed since health care information was first digitized. In general, PIM is conducted in one of two environments: either shared identifiers are present or they are absent. When shared identifiers exist, the main PIM strategy that has emerged is to assign a unique patient identifier (UPI) to each patient. In situations where shared identifiers do not exist, the most common PIM strategy is to use patient matching algorithms to determine whether two sets of information belong to separate patients or the same patient.

2.1. When Shared Identifiers are Present - Unique Patient Identifier

2.1.1. Definition and Context

One of the most straightforward PIM strategies is the creation of a unique health identifier for individuals, or a unique patient identifier (UPI). Generally, a UPI is defined as a "unique, non-changing alphanumeric key for each patient"[6] in a health care system, and which is associated with each medical record or instance of health care data for that patient. Some proposed desirable characteristics of a UPI include that it be unique, non-disclosing[v], invariable, canonical, verifiable, and ubiquitous.[7]

The concept of a *universal* UPI (i.e., a UPI that is assigned to a patient for life, and is consistent across all electronic healthcare systems in the U.S.) has been discussed and debated for a number of years. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 called for the adoption of "standards providing for a standard unique health identifier for each individual, employer, health plan, and health care provider for use in the health care system."[8] Since the passage of HIPAA, the concept of a UPI has generally been welcomed by the health care industry, which views it as a tool to reduce administrative workload and increase efficiency in exchanging electronic health data.[9] Other groups, including private citizens and experts attending a National Committee on Vital and Health Statistics hearing in July 1998, have expressed serious concerns about the effects that a universal UPI might have on patient privacy and data security.[10] These concerns have halted further efforts at creating a UPI in the United States until appropriate privacy legislation is in place[11, vi] even though recent research has argued that adoption of a universal UPI would actually strengthen patient privacy and security (by limiting the number of access points to patient health care data) and, while requiring a significant upfront cost, could pay for itself in cost savings from error reduction and administrative efficiency.[12] The adoption of a universal UPI is also viewed by some as the logical next step in strengthening and developing the national health information network.[13]

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[v] In this context, "non-disclosing" means that the UPI does not contain any personal information about the patient, such as date of birth or social security number.

[vi] Privacy and security concerns did not prevent CMS from developing the National Plan & Provider Enumeration System (NPPES) to assign unique identifiers to health plans and health care providers. The National Provider Identifier (NPI) has been implemented since 2006, and a standard identifier has not yet been implemented for health plans. (Available at: https://nppes.cms.hhs.gov/NPPES/Welcome.do. Accessed June 28, 2012.)

2.1.2. Current Uses of UPIs

UPIs have long been used within individual patient registries and datasets, especially those with prospective data collection, to track and link a particular patient's data over time. One of the most familiar types of UPI is a medical record number – a unique number assigned by a hospital or physician practice that links a patient with their medical record at that institution. Some hospitals have multiple electronic health information systems (e.g., EHRs, administrative/billing systems, lab systems, pharmacy dispensing systems) that assign UPIs to the patients within their domains, and a patient may not necessarily have the same UPI from system to system. Many patient registries also assign a UPI to patients upon screening or enrollment, and UPIs remain the simplest and most straightforward way to uniquely identify patients in a controlled dataset.

UPIs have also been used on a slightly larger scale in aggregated datasets and to link existing databases with administrative datasets. For example, the National Database for Autism Research (NDAR) aggregates data from many different collections of autism data and biospecimens and generates a global unique identifier (GUID) for each patient represented in the aggregated dataset.[14] Similarly, in 2008 the Society of Thoracic Surgeons (STS) Database began collecting HIPAA-compliant unique patient, surgeon, and hospital identifier fields to facilitate long-term patient followup via linking to the Social Security Death Master File and the National Cardiovascular Data Registry.[15]

Outside the United States, UPIs have been used on a wider scale. In Sweden, for example, the personal identity number (PIN) is a unique administrative identifier assigned to all permanent residents in Sweden since 1947. The PIN is used to track vital statistics and also link patients between several national-scale patient registries, including the Patient Register (containing inpatient and outpatient data), Cancer Register, Cause of Death Register, Medical Birth Register,[16] and Knee Arthroplasty Register.[17] In England, a new health identifier was introduced in 1996 – the NHS number is a 10-digit unique identifier used solely for the purpose of patient identification.[18]

2.1.3. Future Directions for UPIs

Recently, interest in expanding the use of existing administrative identifiers (such as the Social Security Number in the United States) to serve as UPIs in the healthcare arena has increased. In 2009, the U.S.-based non-profit Global Patient Identifiers proposed the Voluntary Universal Healthcare Identifier project, which aims to make unique healthcare identifiers available to any patient who uses the services of a regional health information organization (RHIO) or health information exchange (HIE).[19] In May 2011, production deployment on the system began. The voluntary nature of this project and its capacity for patients to have both an "open" voluntary identifier and a "private" voluntary identifier (which can be used to control which caregivers have access to clinically sensitive information) make it an interesting alternative to a mandated universal UPI that would likely be assigned and administered by a Federal government agency. In March 2011, the eCitizen Foundation began requirements-gathering work on the Patient Identity Service Project, an open-source, open standards-based patient identity service that will be able to identify and authenticate a patient across multiple systems to gain access to their health records and services.[20] The project is funded by the OpenID Foundation of Japan, and future goals include research and development, design, implementation, and testing of the service.

2.1.4. Registries and UPIs

UPIs offer a straightforward way to identify specific patients within a particular registry. However, the implementation of a universal UPI in the United States has been halted by concerns over patient privacy, security, and confidentiality, which are unlikely to be resolved soon.

In Sweden, the ability to link data from separate national patient registries using the PIN has allowed researchers to pull from a pool of millions of Swedish residents to address difficult epidemiological questions. Concerns about patient privacy and confidentiality have been addressed by requiring that an ethical review board review and approve the planned study before any data are released to researchers. Past precedent has been that the review boards allow most PIN-based registry linkages, on the condition that the PINs are removed from the combined dataset and replaced with different, unique serial numbers. Researchers also sign a legal agreement ensuring secure storage of the data and agreeing not to attempt to re-identify the patients in the de-identified dataset they are given.[21]

2.2. When Shared Identifiers are Not Present - Patient Matching Algorithms

2.2.1. Definition and Context

In the absence of a national UPI in the United States, most researchers and hospital administrators have turned to patient matching algorithms and other statistical matching techniques as a way to manage patient identities within the confines of a specific patient registry, research project, institution, or other grouping of healthcare data. This method of PIM involves comparing identifiable patient attributes (often demographics such as date of birth, gender, name, and address, but sometimes other individually-identifiable information) using a logic model which then classifies each pair as a match, a non-match, or a possible match that may require manual review.

In the realm of patient and record matching, algorithms can be either deterministic or probabilistic. Deterministic algorithms are more straightforward and classify a pair of records as a match if they meet a specified threshold of agreement. The definition of agreement can vary depending on which data elements are available, the quality of the data (including the level of missing data), and the desired sensitivity and specificity of the algorithm. Probabilistic algorithms treat the match status of individual data elements as observable variables and the match status of the record pair as a latent variable, and model the observable variables as a pattern mixture. This method characterizes the uncertainty in the matching process, making it a more sophisticated (and less straightforward) method than deterministic matching.[22]

One major consideration in choosing an appropriate matching algorithm is the accuracy with which it matches patients. Matching accuracy is affected by the number of patients being compared, the number and type of common data elements being compared, and the mathematical validity of the algorithm itself. An algorithm that returns close to 100% matching in a pool of few patients with many data elements may perform less accurately in a pool of many patients with fewer data elements. Importantly, an algorithm that does not perform accurately may limit the conclusions and results able to be drawn from a particular dataset.

2.2.2. Current Uses of Patient Matching Algorithms

Patient matching algorithms are widely used when disparate healthcare data sources are combined and no unique, common patient identifier is available. The two main options are to use an existing record linkage software program or to develop a new matching algorithm independently. Commercial software options,

such as Link Plus and The Link King, apply probabilistic algorithms that have been found to provide a higher sensitivity than matching using a basic deterministic algorithm.[23] As described in Case Example 37, an open-source product (Febrl) was used to combine data from eleven different data sources into KIDSNET, a computerized registry that gives providers an overall view of children's use of preventative health services.[24] Case Example 38 describes a different approach to patient matching.

Many patient matching algorithms have been developed to meet the needs of specific projects. For example, a group at Partners HealthCare developed an algorithm to compare data in the Social Security Death Master File with demographic data in the Partners EHR system to identify patient deaths that may have occurred outside of Partners institutions (and therefore not recorded in the patients' medical record). They then developed another algorithm using clinical data to identify false-positives resulting from the first algorithm (e.g., if clinical data for a 'deceased' patient is recorded more than 30 days after the date of death in the SSDI, that patient must have been falsely matched to an SSDI entry).[25] In another example, researchers at the University of Alabama Birmingham used matching algorithms to link emergency medical services (EMS) data with hospital EHRs and a statewide death index to characterize the medical conditions and comorbidities of patients who receive out-of-hospital endotracheal intubation.[26]

New and innovative algorithms that are unrelated to specific projects also continue to be developed, with the goal of advancing patient matching algorithm science. Recent examples include algorithms proposed by groups at Vanderbilt University,[27] John Radcliffe Hospital in the United Kingdom,[28] and the University of Duisburg-Essen in Germany.[29]

2.2.3. Future Directions of Patient Matching Algorithms

Any statistical matching approach is dependent on three factors, which are listed below.

1. **The quality of the data it is comparing.** Are the data entered correctly, without mistakes? Are the data complete, or is there a high level of missing data? The quality of data within a particular registry will always be a factor of the practices employed by that registry. See the Chapter 11 for recommended best practices.
2. **The comparability of the data it is comparing.** Are the data from the different sources collected in the same format and in the same way? There are a number of current initiatives to improve the standardization of data elements being used in patient registries,[30] but the area with the most need for future work is the testing and standardization of the algorithms themselves.
3. **The accuracy of the matching algorithm.** What is the likelihood of the algorithm returning a false positive match or missing true matches? While there has been some scientific research validating specific matching algorithms,[31,32,33] the Health Information Technology Policy Committee recently called for increased standards around patient matching, including standardized formats for demographic data fields; internal evaluation of matching accuracy within institutions and projects; accountability to acceptable levels of matching accuracy; the development, promotion, and dissemination of best practices in patient matching; and supporting the role of the patient.[34]

Another emerging trend in patient matching algorithms is privacy-preserving record linkage, or "finding records that represent the same individual in separate databases without revealing the identity of the individuals."[29] This concept was expanded upon by researchers at University of Duisburg-Essen in Germany, mentioned in the previous section, who propose a method that encrypts patient identifiers while

allowing for errors in identifiers. Given the concerns about patient privacy and confidentiality surrounding patient identity management, this method may be increasingly used in the future.

2.2.4. Registries and Patient Matching Algorithms

As mentioned above, patient matching algorithms have become the default PIM strategy for registries that link with outside data sources, due to the lack of a universal UPI in the United States. As a result, many different algorithms have been developed – some are commercially available, some are open-source; some were developed for specific projects and some were developed with broader applications in mind. The performance and effectiveness of matching algorithms can impact the results produced by the registries that are using them. The type of registry also impacts the type of patient matching algorithm needed. Registries used for direct patient care may require an algorithm with different sensitivity, specificity, and timeliness than registries used for population-based research efforts. Registry owners and operators would benefit from standards surrounding patient matching algorithms, which would allow them to more confidently and effectively use appropriate algorithms for linking projects.

3. Emerging Strategies and Related Ideas

In addition to a universal patient identifier and patient matching algorithms, other strategies are emerging to manage patient identities in disparate electronic health care data sources, including biometrics and master patient indices. In the technical realm of patient-centric document exchange, health information exchanges (HIEs) are becoming increasingly important in providing the interoperability infrastructure for successful EHR implementations within and across affinity domains.

3.1. Biometrics

One new option in the PIM field is the use of biometrics – that is, "automated methods of recognizing an individual based on measurable biological (anatomical and physiological) and behavioral characteristics."[35] Some examples of biometric measurements are: fingerprint, palm print, hand geometry, DNA, handwriting, finger or hand vascular pattern, iris/retina, facial shape, voice pattern and gait.

Biometrics are attractive because of their difficulty to fabricate, their resistance to change over time (unlike demographic information such as name and address), and their high degree of uniqueness – making them effectively biological UPIs. For biometrics to be used as UPIs, though, there would need to be agreement on which biometric to use and the format in which it should be collected. Also, some biometric measurements are more unique than others. For example, a fingerprint is highly unique to an individual while a person's hand geometry is not as unique. Hand geometry therefore is often used to confirm a person's identity (i.e., in combination with another identifier) rather than as a sole identifier.

One drawback to using biometrics is the investment in specialized technology and equipment that is required to capture many of these measurements. There is also concern about the privacy and security implications surrounding using biometrics, connected with their history of use in law enforcement and their potential misuse to derive information other than identity (e.g., analyzing DNA for genetic diseases).[36]

Some hospitals have begun using biometrics to verify provider identity and restrict access to EHRs. Biometrics are also being used in some hospitals to verify patient identity upon hospital admission[37] and to identify critically injured, unconscious patients presenting to an emergency room.[38]

Many registries, particularly those with biobanks associated with them, already collect biometric data (e.g., DNA). However, the data are often used for purposes other than PIM, including investigating genetic components of disease[39] and risk factors for disease.[40]

Biometrics remains an attractive option for PIM; the largest obstacle to their use in patient registries is likely the investment in technology and equipment that they require, although this would vary depending on where registry data are collected. A multi-site, practice-based registry would probably be less able to accommodate the collection of biometrics, while a registry based out of a single hospital that already collects biometric data for other purposes would be able to begin collecting biometrics for a registry more easily, since the initial investment in technology has already been made. Registries using biometrics would also be subject to the same concerns about privacy and security as biometric use in other disciplines.

3.2. Master Patient Index

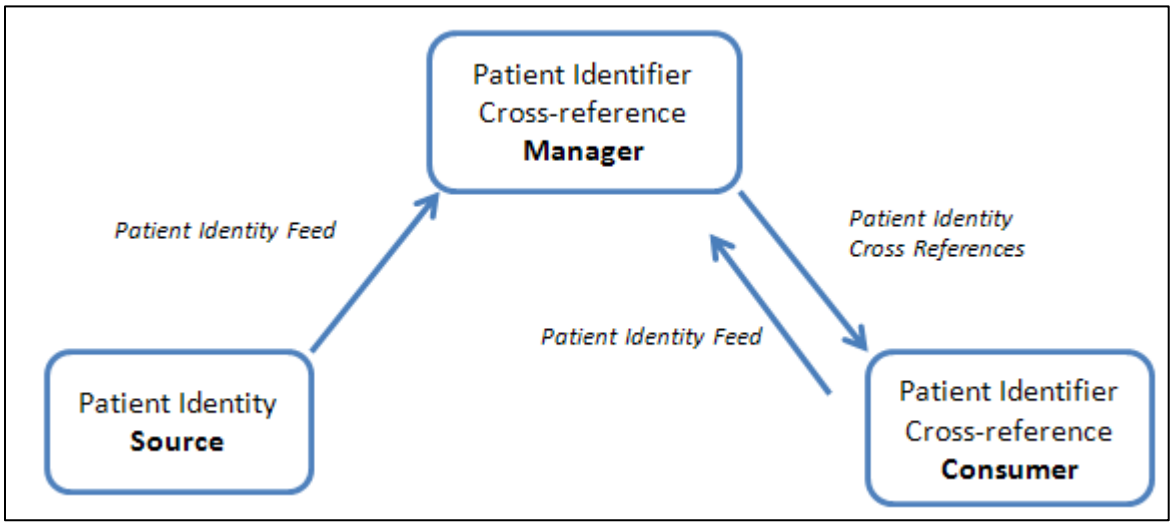
A master patient index (MPI) is an index that facilitates the identification and linkage of patients' clinical information within a particular institution. The term "enterprise master patient index" (EMPI) is sometimes used to distinguish between an index that serves a single institution (i.e., MPI) and one that contains data from multiple institutions (i.e., EMPI). MPIs are not themselves patient identity management strategies, but rather informational infrastructures within which those strategies are applied. Most MPIs use a patient matching algorithm to identify matches and then assign a UPI that is associated with that patient record going forward. MPIs and EMPIs are created for the purpose of assigning a UPI to each patient treated within a certain healthcare system – providers can then use that identifier to have a global view of the patient's care across multiple institutions within that system.

Several leading software companies have released commercially-available MPI and EMPI products. Oracle has published a thorough description of the design and functionality of their EMPI product.[41] Open-source options are also available, including one developed by Project Kenai called OpenEMPI.[42]

EMPIs are used as supplemental tools to apply PIM strategies for data sharing efforts such as Health Information Exchanges (HIEs, described in the next section). For example, the Michigan Clinical Research Collaboratory at the University of Michigan created the "Honest Broker" system which serves three functions: facilitating the actual exchange of data between members of the collaboratory for research, maintaining an MPI to manage patient identities within that data, and de-identifying datasets in conformance with HIPAA limited dataset standards.[43]

Figure 11 is adapted from the IHE integration profile[44] and illustrates the actors that participate in the Patient Identifier Cross-referencing profile. The entity often called an MPI is represented by the combination of the Patient Identity Source ("Source") and the Patient Identity Cross-reference Manager ("Manager"). The Source provides patient identity information (Patient Identity Feed) to the Manager. It is common to have multiple patient identity sources, which provide patient ID feeds to the Manager. The Manager is responsible for managing patient identities by detecting matches and creating and maintaining cross-references of patient identifiers across these various sources. The Patient Identifier Cross-reference Consumer ("Consumer") retrieves Patient Identity Cross References or aliases. This allows patients to be linked across multiple systems or domains that use different patient identifiers to represent the same patient.

Figure 11. Basic Process Flow with Patient Identifier Cross-referencing



Illustrating how users may interact with an MPI in daily practice may be helpful. In one possible scenario, an emergency room physician sees a patient presenting at the emergency room with vague and poorly-defined pain who specifically asks to be prescribed narcotics. A new quality improvement program being implemented in this emergency room requires the physician to check the patient's history of filling prescriptions before issuing a prescription for a narcotic drug. The emergency room's EHR system and the hospital pharmacy's electronic dispensing record system each assign their own patient IDs to patients within their systems, and send patient feeds to the hospital's MPI (the Manager in this scenario) each time a new patient ID is assigned. The MPI creates and maintains cross-references of all identifiers for patients and provides the cross-references to consumers who seek that information. The consumer in this scenario would be the emergency room system, which sends the MPI a patient identity cross-reference or demographic query with information about the patient in question. The MPI notifies the emergency room system that the patient identified in the emergency room as "ER703" matches the patient whose pharmacy records are under the pharmacy system identifier "012". The emergency room system then queries the pharmacy system for the identifier "012", and presents the dispensing record data to the emergency room physician.

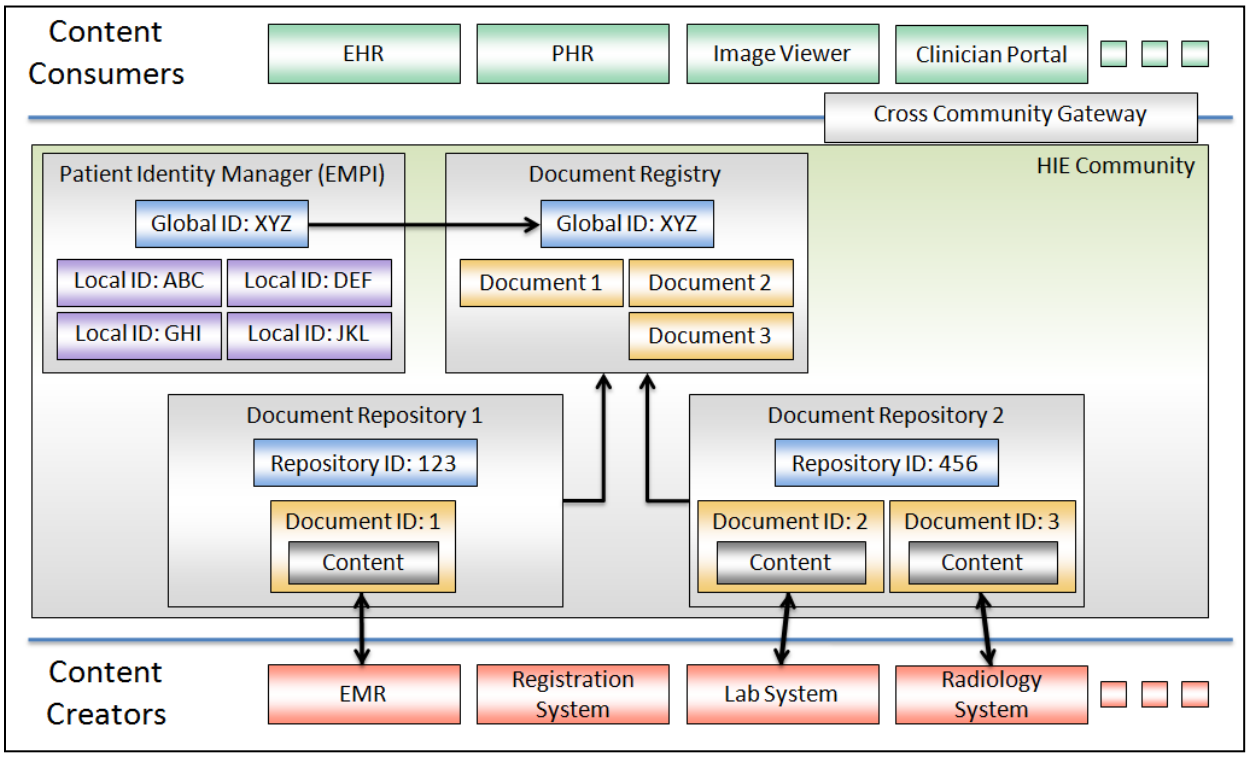
Health care institutions that utilize MPIs to manage patient identities across their multiple data sources (e.g., EHRs, pharmacy records, administrative and billing records) are desirable partners for data linkage projects and for inclusion in patient registries, since they are able to draw from a broader pool of data than any one of the data sources alone. By addressing PIM needs upfront, they minimize the work needed for outside sources to link to their data for research uses.

In the relational infrastructure shown in Figure 11, registries can act as Patient Identity Sources, Patient Identifier Cross-reference Consumers, or both. Registries that contain patient identifiers and other demographic information can act as Patient Identity Sources and send patient identity feeds to a Manager. Registries can also act as Patient Identifier Cross-reference Consumers, if they request and receive patient identity cross references from an MPI or other Patient Identity Cross-reference Manager. This may be done to add new patients to a registry or to augment existing data in a registry with additional information on the same patients.

3.3. Health Information Exchange

A Health Information Exchange (HIE) is an integrated open standards-based solution to enable information sharing across disparate healthcare applications. (See Case Example 31, which describes the Oakland Southfield Physicians HIE.) HIEs are interoperability platforms that provide the means to share patient data produced by health care applications with other applications that consume and use the data, such as EHRs. HIEs implement standards-based health care messages and provide the requisite authentication and auditory services for data governance. HIEs are not themselves patient identity management strategies, but they implement those strategies to manage their data. Most HIEs achieve this by incorporating an MPI to manage and cross-reference the identity of patients within the HIE. See Figure 12 for a graphical representation of the relationship between HIEs, MPI/EMPIs, and data creators and consumers.

Figure 12. Data Flow through a Health Information Exchange[vii]



EHR = Electronic Health Record. PHR = Personal Health Record. EMPI = Enterprise Master Patient Index. HIE = Health Information Exchange. ID = Identifier. EMR = Electronic Medical Record.

Key components of an HIE include:

- Patient Identity Cross-Reference Manager – an implementation of an MPI that cross-references multiple identifiers and serves the linked identifiers, global patient identifier, and unified patient demographics to information consumers and other HIE components.
- Document Repository – clinical document repositories for storing patient records and documents.
- Document Registry – register of patient's documents located in various document repositories.

[vii] © 2010 Health Information and Management Systems Society. Figure reprinted with permission.

- Cross Community Gateway – serves as the entry point for communications between HIE communities.

Content creators who create new patient identifiers provide patient feeds to the Identity Manager which in turn cross-references it to a global patient identifier. Content consumers and creators can query the Identity Manager for the global identifier by providing a subset of patient demographics or one of their local identifiers. This global identifier is used by the document registry to keep track of patient clinical documents. This infrastructure facilitates an interoperable environment that respects data ownership demands but also provides a complete view of the patient's clinical records from multiple sources.

HIEs can be powerful research tools. A group at the Swansea University School of Medicine has developed the Secure Anonymized Information Linkage (SAIL) databank, containing over 500 million records from multiple health and social care service providers in the UK.[45] The SAIL databank has already been used to demonstrate the feasibility of identifying potential clinical trial participants at the primary care level, which may be especially useful for disease areas in which recruitment of clinical trial participants is historically difficult (e.g., chronic conditions such as diabetes).[46]

Because they contain patient data, HIEs are subject to the same privacy and security concerns and regulations as patient registries. A white paper published in April 2011 by the AHIMA/HIMSS HIE Privacy & Security Joint Work Group provides a summary of these considerations.[47]

A patient registry may contribute data to an HIE, but registries and HIEs are distinct and separate endeavors. Data contained in HIEs are not necessarily collected using observational study methods, as patient registry data are – rather, they are often collected and aggregated by linking to existing databases (which may be, for example, registries, administrative databases, or public health surveillance systems). The purpose of an HIE is not just to evaluate specified outcomes in a defined patient population or even to serve any one predetermined scientific, clinical, or policy purpose, but to provide an aggregated database that can be used for a variety of purposes (which may include identifying patients to recruit for clinical trials, or conducting ecological studies, for example).

4. Major Challenges and Barriers

The process of patient identity management introduces several technical, ethical, and operational challenges, including selecting the appropriate PIM strategy, discussed earlier in this chapter. Additional challenges include the obligation to protect the privacy and security of patient data and the technical interoperability (or lack thereof) of disparate health care data sources.

4.1. Protecting Patient Privacy and Security

One of the most pressing challenges in PIM is addressing the tension between linking patient data in order to manage their identities and protecting the privacy and security of those data. This challenge has inherent ethical, regulatory, and technical considerations.

4.1.1. Ethical and Regulatory Considerations

The concepts of protecting patient privacy and security and PIM have always been intertwined. Managing patient identities is essential for protecting the privacy and security of those patients (i.e., in order to protect someone's information, one needs to first know who they are and which information is theirs). Conversely, regulations and ethical considerations compel the protection of patients' privacy and

security when managing their identities (i.e., it is not enough to know who they are and which information is theirs, one must also protect this information).

Many stakeholders in the health information technology field recognize this relationship. The Health Information Security and Privacy Collaboration (HISPC) count patient and provider identification as one of their nine domains of privacy and security.[48] The Commission on Systemic Interoperability released a report in 2005 in which they recommended that Congress authorize the Department of Health and Human Services to "develop a national standard for determining patient authentication and identity," and "develop a uniform federal health information privacy standard for the nation, based on HIPAA and pre-empting state privacy laws […]". These recommendations were made simultaneously, "to advance progress of the connectivity of health information technology."[49] Thus, it is widely recognized that PIM and patient privacy and security are closely related, but there continues to be disagreement about *how they should* relate.

The regulatory framework that guides this discussion in the U.S. is the Health Insurance Portability and Accountability Act (HIPAA), enacted in 1996. As mentioned previously in this chapter, HIPAA mandated the implementation of a nationwide unique patient identifier, but concerns about patient privacy and security prompted the barring of any funding for this endeavor, in 1999. While HIPAA has not led to the implementation of a standard PIM method, it does set forth a framework for the protection of patient privacy and health information security. This framework is summarized in Table 10 in Chapter 7.

In Europe, recently-proposed data protection regulations may have a profound impact on the regulatory environment in which registries conduct PIM activities. The directive proposed by the European Commission in January 2012 includes a provision for the "right to be forgotten," essentially giving individuals the power to remove their personal data from third party data holders at any time they choose.[50] If adopted by the European Parliament and EU Member States, the directive will take effect within two years. The implications that this may have for health care research and registries operating in Europe remain to be seen.

4.1.2. Technical Considerations

Data holders employ three main technical methods of ensuring the privacy and security of patient data: anonymization, encryption, and pseudonymization.

4.1.2.1. Anonymization

Anonymization is the practice of removing information that is identifiable to an individual, or that may enable an individual's identity to be deduced. This is a viable option in some data use situations (e.g., conducting a research study that does not require patient followup), but not an option in others (e.g., maintaining comprehensive health records for patients in an EHR). It is also not a reversible process – once identifiers are removed from data, they cannot be reinserted.

4.1.2.2. Encryption

Encryption involves applying a mathematical calculation or algorithm to transform a patient's original data (plain text) into coded data (cypher text). In order to read the cypher text, a user or system must have access to a key that de-crypts the data back into plain text. This is an attractive option because it does not involve deleting or removing patient data, and because the coded data is not in a readable format if it falls

into the wrong hands. However, encryption requires robust data management policies and resources to implement successfully.[51]

4.1.2.3. Pseudonymization

Pseudonymization is a more sophisticated approach to patient privacy protection. It involves two steps: depersonalization, where identifiable data is separated from other clinical data and stored in a separate location, and pseudonymization, where a unique identifier is generated and applied to the depersonalized dataset. The unique identifier, or pseudonym, does not change for a given patient over time, and is not derived from any identifiable attributes of the patient. Pseudonymization can be reversible, if the relationship between the pseudonym and the identifiable data is maintained in a secure way and can facilitate re-identification of the patient under specific circumstances (e.g., a trusted third party maintains the relationship, and only discloses that relationship if the requestor has knowledge of a particular key or password). Pseudonymization can also be irreversible, where the relationship between the pseudonym and the identifiable data is not maintained, and re-identification is not possible.[52,53]

4.2. Interoperability

In the same way that healthcare enterprises such as hospitals, clinics, and physician offices require patient identifier cross-referencing, that is the linking of patients across different domains, it is necessary to consider how registries may fit within this model and the challenges that level of interoperability may impose. Separate patient registries may use the same PIM infrastructure to register their patient identifiers within a shared patient identifier cross-reference manager, allowing the identifiers to be linked back to relevant healthcare and related systems. This approach may represent a possible solution whereby registries can more easily and securely be linked to other systems across known domains such as an HIE, but challenges still remain in terms of how this approach could successfully be used more broadly across non-participating healthcare enterprises.

5. Summary

Patient identity management is a fast-growing and evolving field, influenced by emerging technologies, regulations, and opportunities to use electronic health care data. The current status of PIM in the United States is primarily a factor of the provision in HIPAA for "standards providing for a standard unique health identifier for each individual […] for use in the health care system,"[54] the debate this provision has generated over implications for patient privacy and security, and the subsequent blocking of any funding being allocated to the pursuit of a national UPI. As a result, most PIM endeavors in the U.S. (including attempts to link patient registries with other health care data sources) utilize patient matching algorithms to identify duplicates and manage patient identities. The lack of standards in this area means that the accuracy and effectiveness of these algorithms can vary widely.

Debate continues around how to best address the challenge of PIM, and stakeholders generally hold one of two views. Some view a national UPI as the best solution, provided the long-standing concerns about protecting patient privacy and security can be adequately addressed in the future. Others believe that resources would be better spent developing and standardizing the PIM methods that have grown organically in the absence of a national UPI – namely, EMPIs and patient matching algorithms. These two endeavors are not necessarily mutually exclusive, and patient registries and data linkage projects would benefit from the advancement of either or both.

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Case Examples for Chapter 17

Case Example 37. Integrating Data From Multiple Sources With Patient ID Matching

Description	KIDSNET is Rhode Island's computerized registry to track children's use of preventive health services. The program collects data from multiple sources and uses those data to help providers and public health professionals identify children in need of services. The purpose of the program is to ensure that all children in the State receive appropriate preventive care measures in a timely manner.
Sponsor	State of Rhode Island, Centers for Disease Control and Prevention, and others
Year Started	1997
Year Ended	Ongoing
No. of Sites	216 participating practice sites plus more than 150 other groups of authorized users
No. of Patients	314,211

Challenge

In the 1990s, the Rhode Island Department of Health recognized that its data on children's health were fragmented and program specific. The State had many children's health initiatives, such as programs for hearing assessment and lead poisoning prevention, but these programs collected data separately and did not attempt to link the information. This type of fragmented structure is common in public health agencies, as many programs receive funding to fulfill a specific need but no funding to link that information with other programs. This type of linkage would benefit the department's activities, as children who are at risk for one health issue are often at risk for other health issues. By integrating the data, the department would be able to better integrate services and provide better service.

To integrate the data from these multiple sources and to allow new data to be entered directly into the program, the department implemented the KIDSNET computerized registry. The registry consolidates data from 8 electronic data sources, in addition to immunization and on-line data entry from 4 more public health programs to provide an overall picture of a child's use of preventive health care services. The sources are newborn developmental risk screening; the immunization registry; lead screening; hearing assessment; Women, Infants, and Children (WIC); home visiting; early intervention; blood spot screening; foster care; birth defects; vital records data; asthma environmental inspection referrals, early child developmental screening, and audiology results. The goals of the registry are to monitor and assure the use of preventive health services, provide decision support for immunization administration, give providers reporting capacity to identify children who are behind in services, and provide recall services and quality assurance.

After being launched in 1997, the registry began accumulating data on children who were born in the State or receiving preventive health care services in the State. Some of the data sources entered data directly into the registry, and some of the data sources sent data from another database to the registry.

The registry then consolidated data from these sources into a single patient record for each child by matching the records using simple deterministic logic. As the registry began importing records, the system held some records as questionable matches, since it could not determine if the record was new or a match to an existing record. These records required manual review to resolve the issue, which was time consuming, at approximately 3 minutes per record.

Without resources to devote to the manual review, the number of records held as questionable matches increased to 48,685 by 2004. The time to resolve these records manually was estimated at 17 months, and the registry did not have the resources to devote to that task. However, the incomplete data resulting from so many held records made the registry less successful at tracking children's health and less utilized by providers.

Proposed Solution

To resolve the issue of patient matching, the sponsor implemented an automated solution to the matching problem after evaluating several options, including probabilistic and deterministic matching strategies and commercial and open-source options for matching software. Since the State had limited funds for the project, an open-source product, Febrl, was selected.

A set of rules to process incoming records was developed, and an interface was created for the manual review of questionable records. Using the rules, the software determines the probability of a match for each record. The registry then sets probability thresholds above which a record is considered a certain match and below which a record is considered a new record. All of the records that fall into the middle ground require manual review.

Results

After considerable testing, the new system was launched in spring 2004. Immediately upon implementation, 95 percent of the held records were processed and removed from the holding category, resulting in the addition of approximately 11,000 new patient records to the registry. The new interface for manual review reduced the time to resolve an error from 3 minutes to 40 seconds. With these improvements, the registry now imports 95 percent of the data sent to the database and is able to process the questionable records through the improved interface.

Key Point

Many strategies and products exist to deal with matching patients from multiple data sources. Once a product has been selected, careful consideration must be given to the probability thresholds for establishing a match. Setting the threshold for matches too high may result in an unmanageable burden of manual review. However, setting the threshold too low could affect data quality, as records may be merged inappropriately. A careful balance must be found between resources and data quality in order for matching software to help the registry. In addition, matching quality should be monitored over time, as matching rules and probability thresholds may need to be adjusted if the underlying data quality issues change.

For More Information

Wild EL, Hastings TM, Gubernick R. et al. Key elements for successful integrated health information systems: lessons learned from the states. J Public Health Manag Pract. 2004 Suppl:S36–S47.

Case Example 38. Using Patient Identity Management Methods to Combine Health System Data

Description	The clinical breast program at Providence Health & Services – Oregon provides screening, diagnosis, and treatment of breast conditions for women in seven hospitals within a regional health care system. The Providence Regional Breast Health Registry integrates patient data from multiple sources to improve patient care and outcomes, conduct research, and collaborate on national quality initiatives.
Sponsor	Providence Health & Services – Oregon; Safeway Foundation
Year Started	2008
Year Ended	Ongoing
No. of Sites	7 health system hospitals in Oregon
No. of Patients	265,130 encounters as of December 2011

Challenge

Leaders of the clinical breast program at Providence Health & Services-Oregon are interested in collecting patient-level data for reporting performance and outcome measures related to health care quality (e.g., biopsy rates); health services (e.g., screening volumes over time); research questions; and accreditation with the National Accreditation Program for Breast Centers (NAPBC). However, patient data reside in numerous information systems, including the hospital electronic health record, administrative billing systems, imaging systems (e.g., mammography, MRI, ultrasound), and the pathology system. The health system uses a patient corporate number (PCN) that is assigned to each patient in the health system as their patient identifier. Each hospital assigns their own medical record number (MRN) to each patient and a separate encounter number for each visit.

Meeting the reporting and research needs of the breast clinic program requires integrating data from all of these multiple systems as well as managing the identities of patients whose data could be contained in one or all systems.

Proposed Solution

In 2008, the Providence Regional Breast Health Registry was created. Registry data are housed in a structured query language (SQL) database that imports data from the various systems and applies matching algorithms to appropriately group data from the same patient. To make the match, the algorithms take into account the PCN, MRN, and encounter numbers for patients with breast health encounters based on a breast-specific ICD-9 and CPT procedure query. Transformation of data from

different systems is sometimes necessary to allow matching (e.g., changing the patient corporate number from 12 to 10 digits).

Results

The registry contains data on 265,130 patient encounters as of December 2011, continues to collect and integrate data presently, and is expanding across the health system to accommodate data from affiliated clinics. Registry data are used to create quarterly updates on quality and outcomes measures identified by program leadership. For the two hospitals in the health system that are NAPBC-accredited, registry data are used to create their required annual reports on outcomes and benchmarks. Registry data have also been used for research purposes, such as identifying factors related to progression from premalignant to invasive lesions.

Key Point

Registries can take advantage of patient identity management solutions to link data from health information systems, regardless of whether a common patient identifier is present. Such linked data provide opportunities for quality improvement, research, and accreditation.

For More Information

http://oregon.providence.org/patients/healthconditionscare/breast-health/Pages/askanexpertlanding.aspx?TemplateName=Providence+Regional+Breast+Health+Care+Registry&TemplateType=FormsandInstructions

Nelson HD, Wang L, Weerasinghe R, et al. Trends and Influences on Mammography Screening in a Community Health System. Poster presented at: Women's Health 2011: The 19th Annual Congress. April 1-3, 2011, Washington, DC.

Soot L, Weerasinghe R, Wang L, et al. Core Needle vs. Surgical Excision Breast Biopsy in a Community-based Health System. Poster presented at: 13th Annual Meeting of the American Society of Breast Surgeons; May 2–6 2012; Phoenix, AZ.

Soot L, Weerasinghe R, Nelson H, et al. How often are High-risk Breast Lesions on Initial Core Biopsy Upgraded after Subsequent Excisional Biopsy? Poster Presentation at American College of Surgeons meeting, Chicago, October 2012.

Chapter 18. Analysis of Linked Registry Datasets

1. Introduction

This chapter provides a review and discussion of the analytic challenges faced by studies that use existing administrative databases and patient registries. The chapter provides additional detail and examples of the issues raised in Chapter 13. While that chapter focuses on the analysis of registry data in accordance with the registry's purpose and objectives, this chapter tackles the issues and opportunities that arise when using registry data, often in combination with other data sources, to investigate hypotheses or questions that are secondary to the original reason for data collection. Case Examples 39 and 40 provide real-world examples of the analysis of linked registry data sets.

The use of administrative databases and medical registries to provide data for epidemiologic research has blossomed in the last decade,[1] fulfilling prophecies that date to the mid-1970s.[2] Studies that use data collected for a primary purpose other than research (e.g., administrative databases) or collected for research purposes but used to support secondary studies (e.g., patient registries) have contributed substantial information to understanding the incidence, prevalence, outcomes, and other descriptive characteristics of many diseases. For simplicity, this chapter will refer to all such studies as "retrospective database studies." Retrospective database studies have also contributed information to understanding disease etiology, patterns of treatment and disparities in care, adverse effects and late events associated with disease treatments, and the comparative effectiveness of some therapies. Despite these achievements, retrospective database studies sometimes receive criticism because of the potential for them to yield invalid results.1,[3] Weiss, for example, points out the potential for retrospective database studies to ascertain exposures, outcomes, and potential confounding variables with poor accuracy, or to provide an invalid reference group (unexposed in a cohort design or controls in a case-control design). Ray provides a table of potential pitfalls in "automated database studies," which includes a similar warning about inaccurate measurement of exposure, outcomes, and covariates, the potential for unmeasured confounding and missing data, and the potential to include immortal person-time.[4]

While these examples and lists of pitfalls provide valuable guidance, none is unique to retrospective database studies. Nonrandomized studies of all designs are susceptible to systematic errors arising from mis-measurement of analytic variables,[5] unmeasured confounding,[6] and poor choice of reference group.[7,8] Also, immortal person-time bias is not limited to secondary research studies; it has even plagued a secondary analysis of data gathered in a randomized trial.[9,10] Taking a different approach, this chapter begins with a review of the fundamentals of sound study design and analysis. These fundamentals apply to epidemiologic research nested in any study population, but the chapter will focus on and illustrate the topics with examples that use retrospective database studies. In the subsequent sections, important considerations in retrospective database studies will be discussed, with the recognition that studies nested in other study populations may have the same considerations, but perhaps less often or to a lesser degree than retrospective database studies.

2. Fundamentals of Design and Analysis in Retrospective Database Research

2.1. Statement of Objective

Most productive epidemiologic research begins with a clear statement of objective. This objective might be descriptive, such as to measure the incidence of a particular disease in some population, to characterize the patterns or costs of treatment for a particular disease in some population, or to measure the occurrence of outcomes among patients with a particular disease. The objective might also involve a comparison, such as to compare the incidence of a particular disease in two or more subgroups defined by common characteristics (e.g., etiologic research), to compare the cost or quality of care for a particular disease in two or more subgroups (e.g., health services research or disparities research), or to compare the rate of outcomes among two or more subgroups of patients (often defined by different types or levels of treatment) with a particular disease (e.g., clinical research). In all cases, the overarching objective is to obtain an accurate (valid and precise) and generalizable estimate of the frequency of an outcome's occurrence, or its relative frequency compared across groups.[11] A valid estimate is one that can be interpreted with little influence by systematic error. A precise estimate is one that can be interpreted with little influence by random error. A generalizable estimate is one that provides information pertinent to the target population, the population for which the study's information provides a basis for potential action, such as a public health or medical intervention. Often times the objective will be accompanied by a specific hypothesis (see Chapter 13), although that is less important than a statement of objective.

2.2. Selection of a Study Population

Once the study's objectives have been stated, the next step in the research plan is to select a study population. Selection of a study population requires identifying potential participants in time and place, including inclusion/exclusion (admissibility) criteria related to the study's objectives and feasibility. Admissibility criteria related to the study's objectives include focusing on a clinically relevant study population of persons in whom sufficient events will occur to provide adequate precision for the estimates of disease frequency, and in whom the exposure categories will occur with sufficient frequency to provide adequate precision for the estimates of association. These criteria are also used to exclude persons with characteristics that can introduce significant bias into the estimates of disease frequency or estimates of association, and that cannot be controlled easily or adequately in the analysis. Precision and validity criteria for admissibility pertain to all studies, regardless of whether they are nested in a health database.

Admissibility criteria related to feasibility center on access to the data. Many ongoing cohort studies have established procedures for data sharing. Similarly, most publicly-funded health databases have established procedures for data access. Investigators must ordinarily provide a statement of the study's objective, a protocol for data collection from the database and for data analysis, a list of persons who will have access to the data, and a study timeline. Some databases charge a fee for data access, although many do not.

An advantage of retrospective database studies is the potential to study associations between rare exposures and rare outcomes in a population large enough to provide sufficient precision, with nearly complete followup, and with few exclusion criteria pertaining to age, comorbidity, or other factors that sometimes limit participation in clinical trials.[12,13] For example, surveillance databases that monitor adverse events potentially associated with pharmaceuticals identified signals suggesting that use of HMG

Co-reductase inhibitors (statins) might increase the risk of amyotrophic lateral sclerosis (ALS).[14,15] The only available epidemiologic evidence came from pooling 41 randomized trials, in which ten ALS cases occurred among 56,352 persons assigned to placebo and nine ALS cases occurred among 64,602 persons assigned to the statins arm.[15] Using Danish databases, a case-control study identified 556 cases of ALS or other motor neuron syndromes and 5560 population controls.[16] The odds ratio associating disease occurrence with statins use was 0.96 (95% CI=0.73, 1.28), thereby rapidly and cost-efficiently providing evidence to counter the drug-monitoring studies and with far greater precision than provided by the pooled clinical trials.

Selection of a study population inevitably involves balancing accuracy and generalizability concerns, as well as cost and feasibility considerations. For example, restriction is one of the most effective strategies for control of confounding through study design.[17] If one is concerned about confounding by sex, a simple and effective strategy to control that confounding is to restrict the study population to a single sex. However, such restriction reduces the study's precision by decreasing the sample size, and may also reduce the generalizability of the results (only applicable to half of the target population). An alternative would be to include both sexes and to stratify the analysis by sex. While this approach would improve the generalizability of the results, and allow an evaluation of confounding, the precision of the estimated association would be reduced, and perhaps substantially reduced, if the estimate of effect in men was substantially different from the estimate of effect in women. In this circumstance, the study becomes effectively two studies.

2.3. Definition of Analytic Variables

The protocol for an epidemiologic study should provide a clear, unambiguous definition of the study's outcome, a description of how it will be measured, and a discussion of the accuracy of that measurement. When sensitivity of a dichotomous disease classification is non-differential and independent of any errors in classification of exposure categories, and there are expected to be few false positives (near perfect specificity), there will usually be little bias of a ratio measure of association.5 This exception to the rule that "non-differential misclassification biases towards the null" has important design implications. It suggests that retrospective database studies should be designed to optimize specificity; in fact, to ideally make the specificity perfect so there will be no false positives. Such a design might require more stringent criteria applied to the outcome definition than are ordinarily applied in a clinical setting, and therefore more stringent than might be found in a disease registry. For example, the estimated prevalence of dementia in a cohort of men and women aged 65 years or older varied by a factor of ten depending on the diagnostic criteria that were applied.[18] Strategies to reduce inclusion of false-positive cases can include requiring evidence in the patient record of medical procedures (e.g., cholecystectomy for gallstone disease or podiatry examination for diabetes) or interventions (e.g., insulin or glucose lowering medications for diabetes) that provide greater confidence in the validity of the case-finding definition.[19] Such an approach often results in fewer included cases and reduced precision, but improved validity.[20]

If the study objective is to compare the frequency of outcome across subgroups, then the protocol should provide a definition of the exposure contrast(s). It is critical that both the index condition (i.e., the "exposed" or "treated" group) and the reference condition (i.e., the "unexposed" or "untreated/placebo" group) are well defined.7,[21] One frequent shortcoming of epidemiologic research is to compare the occurrence of disease in an index group with the occurrence of disease in all others who do not satisfy the index group definition. Studies of this design are easily constructed with retrospective database research,

because of the abundance of participants who do not meet the index group definition. This "all others" reference group is therefore usually a poorly defined mixture of persons.[22] For example, if one uses a pharmaceutical registry to compare the incidence of a disease in statins users with the incidence of disease in those who do not use statins, the reference group of non-users will contain persons with indications for statin use but who have not been prescribed statins, as well as persons without indications for statins use. Non-users also differ from users in the frequency of contact with medical providers, which raises the potential for differential accuracy of ascertainment of health outcomes. It is therefore preferable to first ensure that the reference group of non-users contains persons with indications for use of the treatment,[19] and if possible, are receiving alternative therapies for the same indication.[23] If one has a biologic basis to separate statins into categories, such as hydrophilic and hydrophobic statins, then a comparison of users of hydrophilic statins with users of hydrophobic statins would often be more valid. With these definitions, only persons with indications for statins, and treated with statins, are included in the analysis, thereby reducing the potential for confounding by indication and differential followup.[24]

Last, considerable attention should be given to identifying and accurately measuring potential confounders and effect modifiers.5,[25] The opportunity to examine important etiologic questions with considerable precision has expanded significantly with the availability of large databases, but systematic error due to confounding by unmeasured or poorly measured confounders remains a central concern. Fortunately, databases generally capture inpatient and outpatient clinical events and medication use that can characterize co-morbidities and health care resource utilization, which can aid in the control of confounding. As discussed further below, information on behavioral and lifestyle factors (e.g., cigarette smoking, alcohol use, diet) is infrequently captured or is poorly measured in many databases. Thus, retrospective database researchers should carefully consider the available information on confounders before initiating studies. When data on critical confounders cannot be obtained in a database, and cannot be obtained by linking to another data source, an alternative dataset might be better suited to accomplish the study's objectives. Alternatively, in the presence of unmeasured confounding, researchers can use bias analysis6,[26] to assess the potential impact of residual confounding on their observed findings.[27,28]

2.4. Validation Substudies

The goal of quality study design and analysis is to reduce the amount of error in an estimate of association. With that goal in mind, investigators have an obligation to quantify how far they are from this goal, and bias analysis is one method by which to achieve this goal.6,[26] Bias analysis methods require data to inform the bias model, and these data are obtained from internal or external validation substudies. Retrospective database research is often amenable to collection of internal validation data, for example by medical record review. In addition, many databases have internal protocols that constantly validate at least some aspects of the data. The validation data generated by these protocols can provide an initial indication of the data quality. To facilitate data collection for study-specific internal validation studies, investigators should consider the important threats to the validity of their research while designing their study and allocate project resources accordingly. This consideration should immediately suggest the corresponding bias analyses, which then inform the data collection that will be required to complete the bias modeling.

For example, in the study of statin use related to ALS and neurodegenerative diseases described above,[16] the ICD-10 code used to identify cases (G12.2) corresponded to diagnoses of ALS or other motor neuron syndromes. The investigators therefore selected a random sample of 25 persons from among all those who

satisfied the case definition and a clinician investigator reviewed their discharge summaries. The proportion of these twenty-five who did not have ALS (32%) was used to inform a bias analysis to model the impact of these false-positive ALS diagnoses. Assuming a valid bias model, the bias analysis results showed that the null association was unlikely to result from the non-differential misclassification of other diseases as ALS.

In this example, there was no effort to validate that non-cases of ALS were truly free of the disease. Non-cases are seldom validated, because false-negative cases of rare diseases, especially, occur very rarely. Furthermore, validating the absence of disease often requires a study-supported medical examination of the non-case patients, an expensive, time-consuming, and invasive procedure. Prevalent diseases with a lengthy preclinical period and relatively simple diagnostic tests, such as diabetes, are more amenable to validation of non-cases. The ALS example also illustrates that an internal validation study requires protocol planning and allocation of study resources to collect the validation data. A protocol should be written that specifies how participants in the validation sample will be selected from the study population. Participation in the validation substudy might require informed consent to allow medical record review, whereas the database data itself might be available without individual informed consent. These aspects should be resolved in the planning stage, and the analytic plan should include a section devoted to bias modeling and analysis.6

3. Important Considerations

Once an investigator decides to pursue a research objective using a retrospective database study, there are a number of important considerations to evaluate before undertaking the study. These considerations mostly pertain to the quality and completeness of the database,[29,30] and especially to the potential for systematic errors in the database to affect the validity of the study's result.

3.1. Structural Framework for Data Collection

Health databases collect data for various primary purposes[31] and can be categorized as follows: 1) data collected for the purpose of reimbursing health care providers; 2) data collected for the purpose of monitoring care provided to beneficiaries of an integrated health care system; 3) data collected for the purpose of surveillance regarding a particular disease or disease category; 4) data collected for the purpose of surveillance for individuals with a specific exposure; and 5) data collected on persons with a single admission-defining disease or medical procedure. Each has strengths and limitations (presented in Table 24) to consider when evaluating for use in studies.

Databases that collect information for reimbursement (e.g., Medicare, Medicaid, or Ingenix), which are sometimes called "claims" or "administrative" databases, are quite useful for understanding healthcare costs and can provide important surveillance information on clinical practices and outcomes. However, they may be susceptible to systematic errors if data entries are manipulated by the data generators to affect (likely increase) their reimbursement. For instance, certain clinical conditions with high reimbursement rates may be preferentially reported on claims in patients with those conditions, but who present in the hospital or outpatient setting with other clinical issues, particularly if the presenting conditions are reimbursed at lower rates. The accuracy of some claims datasets have been questioned for diagnoses and procedures including dialysis,[32] weight management,[33] neutropenia,[34] heart failure,[35] diabetes,[36] and functional outcomes after prostatectomy,[37] as examples. On the other hand, the accuracy of registered diagnoses can be quite good.[38] The accuracy of the claims data for its intended objective

should therefore be considered, and preferably estimated quantitatively by an internal validation substudy.[39,40] Alternatively, estimates of the accuracy may be available from an analogous study population from the same or a similar claims dataset; an example is an external validation study. Claims data often lack important information on laboratory parameters, diagnostic test results, and behavioral and lifestyle characteristics, which may limit their utility for research in some topic areas.

The second type of database collects information on the health care provided to beneficiaries within an integrated health care system. This system can be a health insurer (e.g., Kaiser Permanente), a benefits program provided to selected individuals (e.g., Veteran's Health Administration), or a national healthcare system (e.g., General Practice Research Database). These databases typically use an integrated electronic health records (EHR) system to capture health care information directly from physicians' offices, hospitals, pharmacies and other sites where care is provided (e.g., infusion centers, surgical centers). The granularity and quality of data captured in these databases is quite good and includes demographic and clinical characteristics, medication use, major clinical events including death, and importantly, results of diagnostic tests and laboratory assays. As with many epidemiologic studies, some databases are limited in their geographic coverage and in the demographic characteristics of their patient populations. This lack of representativeness may affect the generalizability of results from studies nested in them.

The intended purpose of a third set of databases is surveillance of the incidence and outcomes related to a particular disease or disease category. These databases, or surveillance registries, often pertain to infectious diseases, cancer, and end-stage renal disease (ESRD). Surveillance for infectious diseases sometimes recognizes that only a proportion of cases will be reported, but assumes that the sensitivity and specificity of reporting remain constant over time, so that changes in the relative frequency of reported incidence provides a signal regarding the true incidence in the population. Thus, although the data quality is high, the completeness may be low. In contrast, both the data quality and completeness in most cancer registries are quite high, and the motivation for manipulation to influence reimbursement does not exist because the registry data are not used for that purpose. For example, the U.S. Cancer Surveillance, Epidemiology, and End Results (SEER) registry has a history of quality control and improvement dating to its inception in 1973 and has been linked to the Medicare administrative database to provide data on cancer treatments and outcomes. In the United States and some other countries, patients with ESRD (patients receiving chronic dialysis or who are transplant recipients) are guaranteed coverage of all dialysis services including medications, procedures, and hospitalizations. These benefits extend throughout the patient's life and require significant resources. As such, countries have established surveillance programs, such as the United States Renal Data System (USRDS) to monitor the health care provided to these patients and the costs associated with their health care.

The fourth type of database collects data on patients with a common exposure, and is commonly used as part of a postmarketing pharmacovigilance program related to a biologic or pharmaceutical product or a medical device. This type of database is typically designed to monitor the incidence of adverse events related to the exposure. These databases are often patient registries.

A last type of database is a clinical patient registry of persons with a single admission-defining disease or medical procedure. In fact, the first known health-related registry was the Leprosy Registry in Norway, initiated in 1856. In keeping with this history, many of the current clinical registries are found in Scandinavia. For example, the Danish government supports clinical databases used for quality assurance

and research (e.g., breast cancer, colorectal cancer, hip arthoplasty, and rheumatologic diseases), as well as disease registries (e.g., the multiple sclerosis registry) used for monitoring and research.[41] In fact, a central objective of disease-specific registries may be to provide an infrastructure for clinical trials pertaining to treatments for the disease. The main advantage of these registries and databases is the quality of data on disease characteristics, received treatments, and outcomes related to the disease. The main disadvantage is that they are difficult to use for studies of etiology of the disease that initiates membership in the registry, since the registry includes only persons with the disease.

Table 24. Types of Databases Used for Retrospective Database Studies, and Their Typical Advantages and Disadvantages

Database Type	Strengths	Limitations	Examples
Reimbursement purposes ("claims" data)	– Population-based – Captures inpatient and outpatient clinical events – Captures mortality data – Captures oral & injectable medication use – All claims are adjudicated	– Specific patient populations (65+ yrs old/disabled; employed) – Limited information on subject characteristics (e.g., lifestyle factors) – Does not capture laboratory or test results – Missing medication use in the hospital – Reflects regional practices	– Medicare – Ingenix – Marketscan
Monitor health care provided to beneficiaries	– Population-based – Captures inpatient and outpatient clinical events – Captures oral & injectable medication use – Captures subject characteristics (e.g., BMI, smoking, blood pressure)	– Limited racial and ethnic diversity – Specific health care practices (e.g. selected formulary)	– Nordic Hospital Registries (Denmark, Sweden, Finland) – Kaiser Permanente, Group Health Cooperative, General Practice Research Database (GPRD)
Disease or disease category surveillance	– Population-based – Captures granular disease-specific data (e.g., cancer stage) – Captures outcome events	– Variable amounts of health care utilization information – Limited information on subject characteristics (e.g., lifestyle factors)	– SEER, SEER-Medicare – USRDS
Exposure surveillance	– Prospectively designed – Typically collects granular information on relevant covariates – Designed to capture all potential drug-related adverse events	– Limited information on comparator treatments	

Database Type	Strengths	Limitations	Examples
Quality assurance or research regarding patients with a single admission-defining disease or procedure	- High-quality data on the index disease or procedure - High quality data on the treatment and outcomes associated with the index disease or procedure - Potential to link with other data sources to obtain more complete data	– Absence of an equivalent comparison group without the index disease or procedure – Limited data on health conditions and treatments not related to the index disease or procedure – Limited data on behavioral health (tobacco, diet, exercise, and alcohol consumption)	– Danish Breast Cancer Cooperative Group – Danish Multiple Sclerosis Registry – Danish Hip Arthroplasty registry

3.2. Changes in Coding Conventions over Time

A common problem with retrospective database research is the impact of changes in coding conventions over the lifetime of the database. These can take the form of diagnostic drift,[42] changes in discharge coding schemes, changes in the definition of grading of disease severity, or even variations in the medications on formulary in one region but not others at different points in time. For example, the Danish National Registry of Patients (DNRP) is a database of patient contacts at Danish hospitals. From 1977 to 1993, discharge diagnoses were coded according to ICD-8, and from 1994 forward discharge diagnoses were coded according to ICD-10. ICD-10 included a specific code for Chronic Obstructive Pulmonary Disease (J44), whereas ICD-8 did not [ICD-8 496 (COPD not otherwise specified) did not appear in the DNRP]. In addition, from 1977 to 1994 the DNRP registered discharge diagnoses for only inpatient admissions, but from 1995 forward discharge diagnoses from outpatient admissions and emergency room contacts were also registered. COPD patients seen in outpatient settings before 1995 were therefore not registered; this excluded patients who likely had less severe COPD on average. The change in ICD coding convention in 1994 and the exclusion of outpatient admissions before 1995 presented a barrier to estimating the time trend for incidence of all admissions for COPD in any period that overlapped these two changes to the DNRP.[43]

The General Practice Research Database (GPRD) is a medical records database capturing information on approximately 5% of patients in the United Kingdom.[44] Information is directly entered into the database by general practitioners who were trained in standardized data entry. When the GPRD was initiated in 1987, diagnoses were recorded using Oxford Medical Information Systems (OXMIS) codes, which were similar to ICD-9 codes. In 1995, the GPRD adopted the Read coding system, a more detailed and comprehensive system that groups and defines illnesses using a hierarchical system. Without knowledge of this shift in coding and how to align codes for specific conditions across the different coding schemes, studies using multiple years of data could produce spurious findings.

3.3. Other Data Quality Considerations

3.3.1. Selection of Registered Population

An important advantage of some retrospective database research is that it is population-based, and therefore provides good representativeness for the target population. However, not all retrospective

database research provides this advantage. For example, the U.S. Veterans Health Administration databases provide an important resource retrospective database research. A recent analysis of persons receiving Veterans Health Administration services in fiscal years 2004 and 2005 reported a mortality rate due to accidental poisoning of about 20 per 100,000 person-years.[45] However, this database includes only U.S. military veterans, a selected subpopulation of the U.S. population, with a higher proportion of men than the overall population, and probably an unrepresentative proportion of other characteristics as well. The rate of accidental poisonings was thus almost twice that of the U.S. general population, after adjusting for differences in the age and sex distributions. Similarly, the Medicare administrative database provides an important resource for retrospective database research, including its links with the SEER cancer registry mentioned above. However, the former includes only Medicare recipients, almost all of whom are sixty-five years old or older, and many variables are unavailable for members of this population who participate in managed health care plans. Whether the lack of representativeness in these two examples, and others like them, affects inference made to the target population depends on the particular topic.

3.3.2. Probability of Registration in Relation to Disease Severity

A second type of incomplete data arises at the level of registered persons, rather than afflicting the whole database. In an earlier example, cases of COPD were registered in the Danish National Registry of Patients in reference to ICD-8 before 1994 and in reference to ICD-10 thereafter. Only inpatient diagnoses of COPD were registered in the DNRP before 1995; inpatient, outpatient, and emergency department contacts were registered thereafter. At no time has the DNRP registered COPD cases diagnosed and treated only by a Danish General Practitioner. The least severe cases of this progressive disease are, therefore, missing from the DNRP throughout its history,[46] and patients treated as outpatients are missing from the DNRP before 1995. Similar problems occur with hospital databases of other progressive diseases such as diabetes, Alzheimer's disease, or Parkinson's disease. Patients treated by their general practitioner will often appear in the hospital database with the proper discharge diagnosis eventually, since these progressive diseases become more severe over time. The less severe cases do not appear in hospital discharge databases, which presents a barrier to studies of population-based incidence or prevalence, as well as accurately identifying whether exposure to a potential etiologic agent preceded the disease diagnosis,[47] since neither the date of first diagnosis by the general practitioner, nor the date of symptom onset, is recorded.

Databases often lack accurate measurements of lifestyle and behavioral factors, such as tobacco use, alcohol drinking, exercise habits, and diet. Some databases can provide proxy measurements of these behavioral factors. For example, poor lung function or diagnosis of COPD is a proxy marker for tobacco smoking history, alcohol related diseases such as cirrhosis or prescriptions for disulfiram can be used as proxy markers for alcohol abuse, and medically diagnosed obesity may be a proxy marker for poor diet and lack of exercise. None of these proxies provides a reliable measure of the actual concept, however. For diseases that can be identified by use of specific medications, one could compare the incidence of that medication use with the incidence in the hospitalization database to estimate the proportion of total cases that are registered. Comparison of the date of onset of the medication use with the date of first outpatient or inpatient diagnosis of the disease would provide an estimate of the typical delay between diagnosis by a general practitioner and progression of the disease to a severity level treated in the outpatient or inpatient setting.

3.3.3. Missing Data

Item non-response and missing data at the level of an individual record are often less of a problem for retrospective database research than for comparable cohort studies. Cohort studies that rely on participation by study subjects are subject to attrition and non-response. Attrition occurs when participants early in the cohort's followup stop replying to regularly mailed surveys, telephone interviews, or emailed data collection instruments. These losses to followup are sometimes related to exposure characteristics and health outcomes, which introduces a form of selection bias,[48] even if subjects rejoin the study at a later time.[49] Item non-response occurs when a participant answers a survey or interview, but does not provide a response for one or more of the data fields. Item non-response can also occur when data on an exposure or outcome are collected by other methods, such as when a biospecimen is unavailable to provide tissue for an assay of a genetic or protein biomarker. This missing data may also be related to exposure and disease characteristics, and can introduce a bias, although reliable methods have been developed to resolve bias from item non-response (missing data) in many circumstances.[50] Likewise, inverse probability weighting can sometimes be used to address selection bias and loss to followup,[51] although it has seldom been implemented to date.

Retrospective database research ordinarily uses data collected for a primary purpose other than research. Item non-response (missing data) is also often less of a concern, since the databases often have inherent quality control methods to assure high data completeness. Missing data can, however, plague retrospective database research in other ways. For example, left truncation is sometimes an important problem in retrospective database research, and is basically a missing data problem (although it can also be conceptualized as an information bias).[52] Left truncation occurs when information required to characterize prevalent exposures, covariates, or diseases precedes the establishment of the database. With left truncation, unexposed persons (e.g., non-users of a medication) may have been users before the database was established and apparently incident cases of a disease may have been diagnosed before the database was established, which would make them prevalent cases. Furthermore, covariate information collected at the inception of the database might have been affected by the medical history before the database was established. For example, blood pressure measured soon after a database began might be affected by blood pressure medications prescribed before the database began. Characterizing this initial measurement as baseline (i.e., preceding the first recorded prescription for blood pressure medications) would fail to account for the effect of the prevalent prescription for blood pressure medications, which was prescribed during the left truncation period.

As a second example, in a study of the association between metformin use and the occurrence of breast cancer, the prescription database used to ascertain use of metformin among diabetic patients was not established until after the medication came to market.[53] Data on use of metformin were therefore left-truncated, which can be conceptualized as a missing data problem for time-varying characterization of metformin use in the years preceding the database (see Ibrahim et al[54] for a review of methods to model time-varying data), or can be conceptualized as the more general problem of having poor sensitivity of ever/never classification of metformin use.

Left truncation is a common problem whenever prevalent conditions may have preceded the establishment of a database. For example, many etiologic epidemiology and clinical epidemiology studies exclude prevalent cases of the outcome at the inception of followup. However, some cases of disease may have occurred before followup began and even before the database's inception, and these

prevalent cases would be impossible to identify unless they also appeared in the database after its inception but before the followup time began. For many prevalent diseases with good survival, contact with the medical system is frequent, so most prevalent cases should be identifiable after the database is five to ten years old. However, the potential for left truncation to mask some prevalent cases of the disease under study should be considered as a question specific to the research topic.

Right censoring can also occur in retrospective database research. For example, studies that use birth registries to ascertain congenital defects usually fail to detect defects that are diagnosed later in life, such as congenital heart anomalies. These defects are usually never recorded in the birth registry, so must be ascertained by some other method. Without such continued followup, the measurement of the outcome is right censored at the date of last followup by the birth registry.

Left truncation and right censoring are specific examples of the more general problem of data gaps. Data gaps occur when databases pertain to only a particular subgroup of the larger population, and membership in that subgroup is dynamic. Examples include persons covered by Medicaid and members enrolled in managed care plans. In both examples, the databases pertain to participants in a health insurance program, and membership in those programs can change frequently. Data are collected only while the participants are members. If membership is lost and restored again later, there will be a data gap. Importantly, membership in these plans might be related to other characteristics that affect health, such as socioeconomic status or employment.[55] Similar problems can arise when there are gaps in residency and the database is based on national health care data, or when persons have health insurance from more than one source.

Data gaps in retrospective database research can also arise when medications are dispensed in the hospital, since many databases do not capture in-hospital medication use, leading to a form of information bias. In drug safety studies examining mortality risk related to the use of a particular medication, missing in-hospital medication use can result in spurious estimates of treatment effects.[56] This bias was illustrated in a case-control study examining mortality risk related to inhaled corticosteroid use from the Saskatchewan, Canada database. Analyses that failed to account for missed corticosteroid use during hospitalization events preceding death or the matched date for controls showed a beneficial effect (RR=0.6, 95% CI: 0.5, 0.73). The RR estimates changed markedly once the missing in-hospital corticosteroid use was included (RR=0.93, 95% CI: 0.76, 1.14 and RR=1.35, 95% CI: 1.14, 1.60).[56] This bias has also been observed in studies of injectable medications in dialysis patients where hospitalization events preceding death resulted in spuriously low effect estimates.[57]

3.4. Confounding by Indication

Confounding by indication may occur in non-randomized epidemiologic research that compares two treatments (or treatment with no treatment).[58] In the absence of randomization, the indications for selecting one treatment in preference to another (or in preference to no treatment) are often also related to the outcome meant to be achieved or prevented by the treatment.[59] For example, randomized trials in younger breast cancer patients have shown that chemotherapy prevents breast cancer recurrence.[60] However, in a nonrandomized study of older breast cancer patients, those who received chemotherapy had a higher rate of recurrence than those who did not, probably because chemotherapy was offered only to the women with the most aggressive cancers.[61] This example is a classic illustration of confounding by indication. Importantly, this study collected complete detailed data on every prognostic marker of

recurrence and all of the other breast cancer treatments, yet adjustment for this detailed suite of variables did not resolve the confounding by indication, even using more advanced methods.[24]

retrospective database research is as susceptible to confounding by indication as any other design, although strategies to reduce the strength of this confounding have been proposed[22] and may be most successful when used in the large study populations often achievable only in databases.[62] Explained here is a special class of confounding by indication, which might arise especially in retrospective database research: time-dependent confounding by indication generated by dynamic dosing.[63] Dynamic dosing refers to the clinical situation in which a medication's dose is titrated (increased or decreased) in response to a changing biomarker or clinical measurement on which the medication acts (i.e., a clinical intermediate).[63] Examples include diabetes medications titrated in reaction to hemoglobin A1c (HbA1c) measurements, erythropoiesis stimulating agents (ESAs) titrated in reaction to hemoglobin levels, blood pressure medications titrated in reaction to systolic and diastolic blood pressure values, and antiretroviral therapy titrated in reaction to CD4 counts. The clinical intermediate is therefore both a consequence of therapy and a predictor of future therapy. Time-dependent confounding arises when the clinical intermediate is also a prognostic indicator.[64] For example, hemoglobin concentration is a time-dependent confounder of the effect of ESA therapy on survival because it is a risk factor for mortality, it predicts future ESA dose, and past ESA therapy predicts future hemoglobin concentration. Dynamic dosing therefore introduces time-dependent confounding of the treatment's association with outcomes in the presence of this structure of confounding by indication.[63]

It is important to recognize that the structure requires the clinical intermediate to be both a causal intermediate and a confounder. If it is only a confounder, such as baseline comorbidity or time-dependent comorbidity, the confounding can be addressed by conventional analytic methods. However, when the causal structure indicates that the clinical intermediate is both a causal intermediate and a confounder, inverse probability of treatment weighting (IPTW) with marginal structural models (MSMs) has been proposed as one method for valid adjustment.[65] Pharmacoepidemiologic studies that have used MSMs to address time-dependent confounding have shown significant improvements in confounding control relative to traditional time-dependent analysis.[66-68] In a study of the effect of highly active antiretroviral therapy (HAART) on time to AIDS, the hazard ratio using standard time-dependent Cox regression to adjust for time-varying covariates such as CD4 count and HIV RNA level was 0.81 (95% CI: 0.61, 1.07). Using an MSM, this effect was strengthened substantially (HR=0.54, 95% CI: 0.38, 0.78), providing stronger evidence of the benefit of HAART.[66] Studies examining the effect of titrated ESA doses on mortality risk in dialysis patients that have used MSMs have found hazard ratio estimates at or below the null,[67,68] whereas results from traditional models found substantially elevated hazard ratio estimates.[67]

3.5. Precision Considerations When Standard Errors Are Small (Over-Powered)

The large size of the study population that can often be included in retrospective database study is both a strength and a limitation. The sample size allows adjustment for multiple potential confounders with little potential for over-fitting or sparse data bias[69] and allows design features such as comparisons of different treatments for the same indication (comparative effectiveness research) to reduce the potential for confounding by indication.[22] Nonetheless, systematic errors remain a possibility, and these systematic errors dominate the uncertainty when estimates of association are measured with high precision as a consequence of a large sample size.[70] When confidence intervals are narrow, systematic errors remain, and/or inference or policy action will potentially result, investigators have been encouraged to employ

quantitative bias analysis to more fully characterize the total uncertainty.[26] Bias analysis methods have been used to address unmeasured confounding,[71] selection bias,[72] and information bias[71, 73] in retrospective database-based research.

A second potential problem is the possibility of overweighting results from retrospective database-based research in a quantitative meta-analysis of an entire body of research on a particular topic. In such meta-analyses, weights are in proportion to the inverse of variance, so large studies carry most of the weight. The variance, however, measures only sampling error; it does not measure systematic error. This problem of large studies dominating the weights pertains to any meta-analysis that includes one or two studies much larger than the others. However, given the large sample sizes often achieved by retrospective database research, the high-weight studies may often come from studies nested in these databases. For example, in a 2004 quantitative meta-analysis of eleven prospective studies of the association between pregnancy termination and incident breast cancer,[74] the two retrospective database studies[75, 76] accounted for 54% of the weight in the meta-analysis, but only 18% (2 of 11) of the studies. Random effects meta-analyses[77] and other weighting methods[78] provide only a partial solution to this potential overweighting, and only in some circumstances. Meta-analysts should therefore consider the potential for retrospective database research to be overweighted in their quantitative summary estimates. A plot of the inverse-normal of rank percentile against the corresponding study's estimate of association and confidence interval provides a visual depiction of the distribution of study results,[79] without undue influence by overpowered studies (see, for example, the aforementioned meta-analysis of the association between pregnancy termination and breast cancer risk[74]).

4. Special Opportunities

As noted earlier, retrospective database research runs the gamut of research topics. There are, however, several research areas to which retrospective database research studies are particularly well-suited.

4.1. Rapid Response to Emerging Problems, With Prospective Data

Retrospective database research is ordinarily secondary to another primary purpose. While the collected data may not be optimized to a particular research topic, it is often possible to use the collected data for rapid response to emerging research problems.[80] The study mentioned above of the association between statins medication and incident ALS is also a suitable example here. Drug surveillance databases had identified a higher than expected prevalence of statins medications associated with reports of ALS. A pooled analysis of trials data revealed no association, but was limited by the small number of ALS cases, short duration of followup, and potential for crossover from the placebo arm to statins treatment after the trial finished.[81] Thus, there was little evidence to evaluate the potential causal association between this highly effective drug class—which prevents the incidence of cardiovascular morbidity and mortality[82, 83]—and the incidence of ALS, a progressive, neurodegenerative, terminal disease.[84]

The precisely measured null association reported in the case-control study[16] provided a rapid and reliable basis to assuage concerns about an etiologic association between statin use and ALS occurrence. Imagine what would have been required for a purposefully designed study to evaluate the association. The pooled trials result had included nearly 120,000 persons observed over more than 400,000 person-years, yet included only 19 cases of this rare disease. Few existing cohort studies would have had sufficient person-time to expect substantially more cases, and a cohort study designed to evaluate the association would have required a substantial investment of time and financial support.

A case-control study might have been feasible, but imagine the resources required to enroll and interview an equivalent number of ALS cases as were included in the database study (~550) and their matched controls. Furthermore, a case-control study of this design would likely have been susceptible to recall bias and selection bias.5,8 The retrospective database research study avoided both of these biases.[16] Recall bias was avoided by ascertaining statins use from a prescription database. These prescriptions were recorded before the ALS incidence, so could not have been affected by the subsequent disease occurrence. Selection bias was avoided because all ALS cases in the region during the followup period were included, and controls were selected from the Civil Registration System. Neither case/control status nor use of statins was likely to be associated with participation. Thus, the retrospective database research study on this topic provided a rapid, cost-efficient, and precise result on an important public health topic, which otherwise would have gone unevaluated or would have required a substantial investment of time and finances to achieve an equivalent, or possibly more biased, result. This study provides a good example of the value of retrospective database research in such circumstances.

4.2. Cost-Efficient Hypotheses-Scanning Analyses

Retrospective database research can sometimes evaluate multiple associations with only a marginal increase in cost over the evaluation of a single association. The U.S. Food and Drug Administration's (FDA) Sentinel Initiative will use an active surveillance system within electronic data from healthcare information holders to monitor the safety of all FDA-regulated products.[85] Similarly, the EU-ADR project aims to use clinical data from health databases, combined with prescription databases, to detect adverse drug reactions.[86,87] The project uses text mining, epidemiological, and computational techniques to analyze electronic health records, with the goal of detecting combinations of drugs and adverse events that merit further investigation.

As a second example, Latourelle et al used retrospective database research to evaluate the association between estrogen-related diseases, such as osteoporosis or endometriosis, and the occurrence of Parkinson's disease.[88] To be categorized as "exposed" to these diseases, cases or controls had to have them appear as discharge codes in the hospital database before the first discharge code for Parkinson's disease. For relatively little additional cost, Latourelle et al also evaluated the association between 200 other diseases and the subsequent diagnosis of Parkinson's disease as a hypothesis scanning study, with the objective of suggesting new ideas regarding Parkinson's disease etiology.[88] The analysis adjusted for multiple comparisons using empirical Bayes methods designed to reduce the emphasis on potentially false-positive associations.[89] This potential for cost-effective hypotheses-scanning studies as an explicit objective of retrospective database research should be viewed as a strength of such research, not a limitation, so long as the objective is appropriately labeled as such. Hypotheses suggested by these types of studies are often further investigated using studies designed specifically for the topic.

4.3. Hybrid Designs

Retrospective database research does not necessarily have to be limited to data collection from secondary data sources. Hybrid designs allow the use of database research for some aspects of data collection, and primary data collection for others. For example, a study of drug-drug and gene-drug interactions that might reduce the effectiveness of tamoxifen therapy began by identifying eligible breast cancer patients using the Danish Breast Cancer Cooperative Group's clinical registry.[90] This clinical registry also provided data on prognostic factors such as tumor diameter and lymph node evaluation, and on treatments such as chemotherapy and radiation therapy. Linkage with the Danish Civil Registration System

provided data on vital status, linkage with the Danish National Patient Registry provided data on comorbid diseases, and linkage with the Danish National Registry of Medicinal Products provided data on use of prescription medications. Thus, for relatively low cost, a cohort of breast cancer patients with complete medical, prognostic, and breast cancer treatment data was assembled. A case-control study was then nested in this cohort by identifying cases of breast cancer recurrence and matching controls to them by risk-set sampling.8 Once cases and controls had been identified, their tumor blocks were collected from the Danish National Pathology Registry,[91] and these were used for the necessary bioassays. Thus, retrospective database research allowed identification of the source population, selection of cases and controls, and provided all but the bioassay data. This data, which is expensive to collect, was only obtained for about 13% of the members of the total cohort. This hybrid design demonstrates that retrospective database research will remain an important contributor, even in the era of personalized medicine.

A second example of a hybrid design linked survey data collected over the internet with retrospective database research.[92,93] Participants were recruited by advertisements on web sites likely to be visited by women who intended to become pregnant. They were linked to the study's web site, where they completed an enrollment screening questionnaire followed by an interview covering socio-demographics, reproductive and medical history, lifestyle, and other factors. Enrolled participants were then contacted bimonthly by e-mail for 12 months or until they reported that conception had occurred. Data obtained from the web-based questionnaires were also linked to nationwide databases, which allowed collection of additional data on confounders and outcomes, as well as an assessment of the validity of some of the self-reported data, such as prescription drug use. This study again demonstrated the use of database research, in combination with primary data collection, to provide a cost-efficient resource for collecting some aspects of the study data. In contrast to the previous example, the cohort in this example was enrolled following more typical cohort study strategies, and not by using the databases to identify a source population.

Hybrid designs have also been used to collect data by medical record review for data fields that are available for a subset of participants in a database.[94] Thus, the database provide a cost-efficient resource for initial data collection, which is then supplemented as necessary by medical record review or another primary data collection method to complete the dataset. Once an investigator is open to the potential for hybrid designs and there are retrospective database resources suitable to the research topic, the opportunities for combining the databases with primary data collection are limited only by the investigator's creativity.

4.4. Ample Data Allows for Novel Designs

As mentioned above, the ample data often available from retrospective database research can lead to overweighting of such studies in quantitative meta-analyses. While this problem may be disadvantageous, a compensating advantage is the opportunity to use retrospective database research to implement novel study designs. For example, confounding by indication and other biases often plague clinical epidemiology,[3,24] even in the era of comparative effectiveness research. However, the ample study size often provided by retrospective database research can overcome these threats to validity in some situations. The large sample size might allow a design with carefully restricted exposure groups,1 such as including only new users of a pharmaceutical,[95] whereas conventionally sized cohort studies would not always have sufficient study size to implement such a design. The new user design in turn

facilitates other advanced designs, such as propensity score matching and instrumental variable analyses,[22] which are intended to further counteract these threats to validity. These and other novel designs can be implemented in studies of any size, but are likely most effective when the study size is large.[96]

4.5. Data Pooling Methods

Although retrospective database research often provides relatively large study size within a research topic area, a study's power may still be insufficient if the study must be restricted to rare exposure subgroups or if the study outcome is rare. In these cases, data pooling across similar databases may allow sufficient sample size to provide adequate power, and provides advantages over conventional meta-analyses because they allow simultaneous and consistent data analyses. Such pooling projects face substantial challenges.

First among these challenges is harmonization of the data elements. To pool an analysis, data collected from different databases must be able to provide analytic variables (exposure, confounders, modifiers, and outcomes) with equivalent categorizations and definitions. Such data harmonization can be quite challenging. Harmonization of data elements categorized differently in two or more databases, or that are differentially available, may pose an insurmountable barrier to pooling. For example, one database might include data on behaviors like alcohol and tobacco use, whereas a second database might not. The pooling project would then face the unenviable decision of controlling for these behaviors for some, but not all, data centers (in which case the analysis becomes comparable to a conventional meta-analysis), or abandoning control for these variables at all centers in order to achieve the data harmonization goal. Differences in the conceptual underpinnings of data elements may be more common. Even a variable as conceptually simple as the Charlson comorbidity index[97] can present surprising challenges when subject to harmonization considerations. The Charlson index includes 19 comorbid conditions (e.g., diabetes). As mentioned above, some databases might be able to ascertain diabetes diagnosed in all medical settings (e.g., general practitioner, outpatient, and inpatient), whereas others might be able to ascertain diabetes diagnosed in only a subset (e.g., only general practitioner or only outpatient specialty clinics). Diabetes is defined differently in the different databases, which are not strictly harmonious, and therefore contribute differently to the Charlson index. While the definition of the Charlson variable may be harmonious across the pooled databases, the underlying conceptualization is different, and this difference could result in differences in the strength of confounding by the comorbidity variable or in the degree to which it modifies the association between an exposure contrast and outcome.

Ethical and legal constraints, which are often placed on data sharing, present a second important challenge to pooling projects. Pooling of de-identified datasets can sometimes be arranged through data use agreements, but even these arrangements can be quite challenging and time-consuming. Rassen et al compared four methods of pooling de-identified datasets:[98] (a) full covariate information, which may violate privacy concerns, (b) aggregated data methods, which aggregate patients into mutually stratified cells with common characteristics, but usually delete cells with low frequency counts that might defeat the privacy protections of large frequency counts, (c) conventional fixed or random effects meta-analysis, which provides only summary estimates of association for pooling, and (d) propensity score-based pooling, for which a propensity score summarizes each individual's covariate information. They reported that the last alternative provided reasonable analytic flexibility and also strong protection of patient

privacy, and advocated its use for studies that require pooling of databases, multivariate adjustment, and privacy protection.[98]

More recently, Wolfson et al proposed a pooling method that requires no transfer of record-level data to a central analysis center.[99] Rather, the central analysis center implements statistical computing code over a secure network, accessing record-level data maintained on servers at the individual study centers. Data aggregation occurs through return of anonymous summary statistics from these harmonized individual-level databases, and even iterative regression modeling can be implemented. The advantage is a reduced burden to comply with ethical and legal requirements to protect privacy, since no record-level data are ever transferred. The disadvantages include requirements for strong data harmonization, secure networks that satisfy regulatory oversight, and assurances that no record-level data are transmitted. It is possible that some summary statistics could violate standards for de-identification, but safeguards can be implemented to prevent transmission of such summary statistics.

These new methods for pooling provide exciting opportunities for pooled projects. At the time of this writing, investigators who choose to undertake them should expect delays required to explain the methods to regulators with oversight of data protection, who are not yet familiar with them. In addition, it is likely that implementing the methods for the first few projects will be challenging. With those caveats in mind, the path should be blazed, because once the methods are familiar and reliable, new research opportunities and efficiencies will inevitably arise. Investigator teams without the time, resources, or patience to implement these new methods can ordinarily rely on conventional meta-analysis methods,[100] which solve the privacy protection concerns but also have some important disadvantages by comparison.[98,99]

5. Summary

Retrospective database research has made important contributions to descriptive epidemiology, public health epidemiology targeted at disease prevention, and clinical epidemiology targeted at improving disease outcomes or estimates of disease prognosis. Investigators who conduct retrospective database research should first focus on the fundamentals of epidemiologic design and analysis, with the goal of achieving a valid, precise, and generalizable estimate of disease frequency or association. Beyond the fundamentals, retrospective database research presents special challenges for design and analysis, and special opportunities as well; researchers should be aware of both in order to optimize the yield from their work.

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Case Examples for Chapter 18

Case Example 39. Combining De-Identified Data from Multiple Registries to Study Long-Term Outcomes in a Rare Disease

Description	Four independent, prospective, observational and multi-center disease registries participate in an ongoing systematic review of their aggregated data to study pediatric pulmonary arterial hypertension (PAH). The review is intended to describe disease course and long-term outcomes of pediatric PAH in real-world clinical settings.
Sponsor	Actelion Pharmaceuticals Ltd.
Year Started	2009
Year Ended	Ongoing
No. of Sites	4 multi-center registries
No. of Patients	Approximately 500

Challenge

Pulmonary arterial hypertension (PAH) is a rare disease that is poorly described in pediatric populations. Newly-developed PAH therapies used in the pediatric population have recently led to improved survival, and patients are now likely to reach adulthood. This increased attention on pediatric PAH patients presents new challenges in both data needs and methodology to evaluate disease history and progression, general development, and clinical and treatment experience.

In 2009, Actelion's product bosentan was approved by the European Medicines Agency (EMA) for an expanded indication of pediatric PAH. The sponsor then began working with the EMA to determine how best to collect longitudinal treatment and outcomes data on this population.

Proposed Solution

Four registries that collected data on pediatric PAH patients already existed: one is global in scope and three are national in scope (in the U.S., France, and The Netherlands). The sponsor and the EMA recognized that a compilation of results from these multiple registries within a common systematic review protocol would allow them to examine data from a large number of patients representing a significant proportion of global pediatric PAH patients. After the EMA approved the systematic review study design, the individual registries reviewed the protocol and agreed to participate.

The sponsor contacted the individual registries to evaluate their data collection and analysis practices. As it was not feasible to pool the data due to differences in data collection elements used by the registries, analyses were done by the respective registry data owners using similar methods under the guidance of a common statistical analysis plan. The de-identified summary tables were sent separately to the sponsor to be included in the systematic review reports.

The outcomes of interest are disease course and long-term outcome (e.g., clinical worsening, hospitalization, death) and general development (e.g., height, body mass index, sexual maturation, onset of puberty). The protocol and statistical analysis plan define the study population (all patients enrolled in one of the four registries aged ≤18 years at the time of diagnosis with PAH), observation period, appropriate statistical methods, and standardized procedures for data extraction (including data quality assurance).

Results

Analyses are performed on an annual basis and the same data cut-off date is applied to all registries to define the observation times of analysis (i.e., from Oct 2009 to the annual report's data cut-off date). This effectively creates a new cohort for each annual report, which is a standalone document.

The first annual report was sent to the EMA in 2010. For this first analysis, the sponsor had to address technical challenges related to differences between the registries – for example, three of the registries used the SAS software package to conduct their analysis, and one used SPSS, which produces a slightly different output. For subsequent reports, the sponsor also spent time in dialogue with the registries to clarify the detailed requirements, definitions and analyses of the statistical analysis plan to ensure that each registry understood and interpreted it the same way.

Longitudinal analyses will be examined for evidence of improvement or deterioration over the followup period. The method of analysis respects correlations of within-patient measurements and is based on all patients with at least 2 measurements during the follow-up period.

Key Point

For rare disease populations where registries already exist, systematic review of registry datasets may be a more feasible way to analyze outcomes data rather than creating a new patient registry. When planning and conducting such a study, close collaboration between the parties is important to develop a detailed statistical analysis plan and clarify expectations for registry-level analyses.

For More Information

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Case Example 40. Understanding Baseline Characteristics of Combined Datasets Prior to Analysis

Description	The Kaiser Permanente Anterior Cruciate Ligament Reconstruction (KP ACLR) Registry was established to collect standardized data on ACLR procedures, techniques, graft types, and types of fixation and implants. The objectives of the registry are to identify risk factors that lead to degenerative joint disease, graft failure, and meniscal failure; determine outcomes of various graft types and fixation techniques; describe the epidemiology of ACLR patients; determine and compare procedure incidence rate at participating sites; and provide a framework for future studies tracking ACLR outcomes.
Sponsor	Kaiser Permanente
Year Started	2005
Year Ended	Ongoing
No. of Sites	42 surgical centers and 240 surgeons
No. of Patients	17,000

Challenge

The KP ACLR Registry aimed to collaborate with the Norwegian Ligament Reconstruction Registry on a series of studies to proactively identify patient risk factors as well as surgical practices and techniques associated with poor surgical outcomes. The Norwegian registry has been operating since 2004 and contains data on 12,358 patients. Combing data from these two registries would allow for faster identification of certain risk factors and evaluation of low frequency events.

Proposed Solution

The first step was to compare the patient cohorts of the registries and the surgical practices of the two countries. Aggregate data were shared between the registries in tabular form. Analysis was conducted to identify differences that would be important to consider when making inferences about a population other than that covered by the registry. Commonalities were also identified to determine when inferences could be made from each other's analysis and when data do not need to be adjusted.

Results

The analysis found that the registries generally have similar distributions of age, gender, pre-operative patient reported knee function and knee-related quality of life. Differences were observed between the two registries in race, sports performed at the time of injury, time to surgery, graft use, and fixation type. While these differences should be accounted for in future analyses of combined datasets from

both registries, the results indicate that analyses of the combined datasets are likely to produce findings that can be generalized to a wider population of ACLR patients.

Since this comparison was conducted, two hypothesis-driven analyses have begun, investigating questions using the combined registry datasets. Future plans include further collaboration with ACLR registries in additional countries.

Key Point

Combining or pooling registry data can be a valuable approach to achieving a larger sample size for data analysis. However, it is important to identify cohort and practice differences and similarities between registries before making generalizations of registry findings to other populations or sharing data for collaboration projects.

For More Information

http://www.kpimplantregistries.org/Registries/acl.htm

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Section V. Special Applications in Patient Registries

Chapter 19. Use of Registries in Product Safety Assessment

1. Introduction

Once a drug or device is approved for use by a regulatory authority, the product is generally used by larger and more diverse populations than are typically studied in the clinical trials leading up to approval. As a result, the period after approval is an important phase for identifying and understanding product safety concerns associated with both acute and chronic use. The need for postapproval (also called postmarketing) safety assessment as it exists today was, for the most part, born out of well-publicized product safety issues that were initially detected by clinicians recognizing a pattern of rare serious events, such as phocomelia caused by prenatal exposure to thalidomide[1] and rare vaginal cancers that occurred in young women who had *in utero* exposure to diethylstilbestrol.[2] The detection of serious adverse drug reactions after authorization has led to much debate about the adequacy of both industry and regulatory approaches to preauthorization assessment and testing. However, the decision to authorize a medicine is a balance between wanting to know as much as possible about the safety of a product and the need to make new drugs available for patients.[3] The implication of this is that authorization cannot mean that a medicine is completely safe; rather, it is an assessment that at the time of authorization, the known benefits for the average patient in the approved indication outweigh the known risks. But the degree to which the known risks represent the actual safety profile of a product will depend upon the size, duration, representativeness, and thoroughness of the clinical trial program, which, in turn, is related to the complexity of the patients and the state of knowledge of the disease being targeted. Trials conducted as part of clinical development are, by necessity, of limited duration and size and generally focus on a narrowly defined population that represents only a small segment of the population with the disease or product use of interest. Clinical trial populations tend to be restricted to those who have limited concurrent disease and who are on few, if any, concomitant medications. Typically, trial protocols include lengthy lists of inclusion and exclusion criteria that further restrict the trial population. Unless a drug or a product is intended for a very narrow indication or a very rare disease, it is not feasible to require clinical trials to be inclusive of all types of patients likely to ever be exposed to it. Even in the case of a narrow indication, the potential long-term and delayed effects of a product are unlikely to be established during most clinical trial development programs.

To address the acknowledged limitations of what is known about the safety profile of a product at the time of authorization, postmarketing pharmaco- and medical device vigilance is traditionally, and by regulation, performed through spontaneous adverse event reporting. The exact requirements for spontaneous reporting to the regulatory authorities vary internationally and are dependent upon the country/region, approval type, and product type. It is widely acknowledged, however, that spontaneous reporting captures an extremely small percentage of the actual events occurring, and that, while it is useful for identifying rare and potentially significant events,[4,5] it has limited use in the detection of other equally important types of events, including increases in events with a high background rate. This form of

postmarketing surveillance is reactive in that one waits for adverse events/reactions to be spontaneously reported, assesses them for causality, and estimates the importance of the information.

As well as collecting only an indeterminate fraction of adverse reactions, this method of surveillance depends upon someone reporting the events of interest. There is some evidence that clinicians who report adverse events are not typical of clinicians in general, and other reporters such as patients, lawyers, and consumer groups may have unclear motivations for reporting, which introduces further bias into the equation.[6,7,8]

The current methods available for adverse event reporting are seen by many as burdensome and not amenable to incorporation into a clinician's normal workflow. Waiting for reports to arrive and accumulate may also delay the detection of adverse reactions. On the other hand, a massive uptake of a new drug or device, such as seen with Viagra® (sildenafil citrate) or coronary artery stents, may lead to a sudden flood of reports of nonserious as well as serious adverse events that could potentially overwhelm established systems.

To overcome some of the difficulties associated with managing large databases of spontaneous adverse events, many employ statistical methods to identify signals of disproportionate reporting (SDR). These methods identify adverse events that are reported more frequently with a drug or device than would be expected compared with other event/product pairs in the database and do not imply any kind of causal relationship.[9] It is important to be precise as to what is meant when using the term "signal" or "signal detection" since the terms are ambiguous; in the context of automated methods of detecting statistical anomalies, the term *SDR* should be used.[9] However, these statistical methods may not be reliable in certain situations, such as when there is major confounding or when the increased risk is small compared with the background incidence of the event.[9] All these above-mentioned limitations mean that there are situations when spontaneous reporting may not be adequate as the sole method of postmarketing surveillance.

To address problems with traditional pharmaco- or medical device vigilance when there are particular known limitations of knowledge of the safety profile of a product and/or to further address unresolved safety concerns, some products are approved subject to postmarketing commitments, which may be requested for safety purposes as well as to address other outstanding questions. In Europe, in response to concerns over pharmacovigilance, marketing authorization applicants are required to submit a European Union–risk management plan (EU-RMP) when seeking a marketing authorization for the majority of new chemical entities and biologics. This EU-RMP states what is known and not known about the safety profile of a medicinal product, how its safety profile will be monitored, investigated, and characterized, and what risk minimization activities will be undertaken. While many products will require only routine pharmacovigilance, for others more proactive methods of pharmacovigilance will be necessary to supplement the use of spontaneous adverse reaction reporting and periodic safety update reports. Although additional clinical trials may occasionally be mandated, it is more common for observational pharmacoepidemiologic studies to be conducted to ascertain the safety profile of a product under real-world use.

Other observational methods of tracking and evaluating safety data have historically included active surveillance systems, such as the prescription event monitoring (PEM) systems used in the United Kingdom (Drug Safety Research Unit),[10] New Zealand (NZ Intensive Monitoring Programme), Japan (J-

PEM), and elsewhere targeting new products, and the retrospective use of administrative claims data. In the UK, the requirement that access to most secondary care is through a general practitioner has led to the use of their electronic health care systems for pharmacovigilance purposes; however, this type of integrated approach is not yet widely accessible elsewhere. In May 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, an effort to create an integrated electronic system in the United States for adverse event monitoring, incorporating multiple existing data sources including claims data and electronic medical record systems.[11]

Medical devices in the United States have different surveillance programs from those for drugs. The Safe Medical Devices Act of 1990 requires that high-risk medical devices be tracked after marketing and that product corrections and removals be reported to FDA if actions were taken to reduce health risks. Most medical device safety tracking is accomplished through reports submitted to FDA from medical facilities when devices are implanted or explanted. In addition, hospitals, nursing homes, ambulatory surgery centers, and outpatient treatment facilities are required to report to FDA whenever they believe that a device caused or contributed to the death of a patient, though this reporting is a voluntary requirement and not enforceable or audited.[12]

Whether to comply with a postmarketing requirement or out of a desire to supplement spontaneous reporting, prospective product and disease registries are also increasingly being considered as a resource for examining unresolved safety issues and/or as a tool for proactive risk assessment in the postapproval setting. The advantage of registries is that their observational and inclusive design may allow for surveillance of a diverse patient population that can include sensitive subgroups and other groups not typically included in initial clinical trials, such as pregnant women, minorities, older patients, children, or patients with multiple comorbidities, as well as those taking concomitant medications. In contrast to clinical trials, in which the inclusion criteria are generally tightly focused and restrictive by design, registry populations are generally more representative of the population actually using a product or undergoing a procedure, since the inclusion criteria are usually broad and may potentially include all patients exposed regardless of age, comorbidities, or concurrent treatments. Data collection may lead to insights about provider prescribing practices or off-label use and information regarding the potential for studying new indications within the expanded patient population. Followup duration can be long to encompass delayed risks, consequences of long-term use, and/or effects of various combinations and sequencing of treatments. Such information can be used as a source of publications, to assist the medical community with developing recommendations for monitoring patient safety and product usage, and/or to contribute to the understanding of the natural history of the disease.

There are also many challenges to the utility of registry data for providing more clarity about safety concerns and for prospective risk surveillance. These challenges relate largely to how products are used and the legal, regulatory, and ethical responsibilities of registry sponsors. Most registries that follow specific products do so through cooperation from physicians who prescribe (or implant) these products. Depending on the setup and legal constraints of the registry, sometimes only a subsection of prescribing physicians may be involved in entering patients, a situation that raises questions about the representativeness of the physicians and their patients. However, the registry approach has the potential to be very useful for studying products that are used according to their labeled indications; it also allows for effective surveillance of products that are used off label but by the same practitioners who would use it for the labeled indication. For example, a product might be approved for moderate-to-severe asthmatics

and used off-label in patients with mild asthma, yet the prescribing medical providers would already be included in the registry and could easily provide information about all their product use. Off-label use is much more difficult to study when a medical product is used by a wide variety of medical care providers; for example, drugs that promote wakefulness or are thought to increase a patient's ability to concentrate, acting as immunomodulators. The legal, regulatory, and ethical aspects of registry sponsors also affect whether they are required to report any adverse events that may be observed, since only those legal entities that market (or distribute) a medical product are required to report adverse events. For all other parties, such reporting is ethical and desirable, but not enforceable or required.

The purpose of this chapter is to examine the role of registries as one of the available tools for enhanced understanding of product safety through adverse event detection and evaluation. The role of both registries created specifically for the purposes of safety assessment and of those in which the collection of safety data is ancillary to the registry's primary objectives will be examined. The legal obligations of regulated industries are discussed by others and are only mentioned briefly here. Similarly, issues to consider in the design and analysis of registries are covered in Chapters 3 and 13, respectively. Chapter 12 discusses practical and operational issues with reporting adverse event data from registries. The potential ethical obligations, technical limitations, and resource constraints that face registries with multiple different purposes in considering their role in adverse event detection and reporting are also discussed. Case Examples 41 and 42 offer descriptions of how some registries have provided data for product safety assessments.

2. Registries Specifically Designed for Safety Assessment

Disease and product registries that systematically collect data on all eligible patients are a tremendous resource for capturing important information on safety. Registries commonly enroll patients who are not just different from but more complicated than those included in clinical trials, in terms of the complexity of their underlying disease, their comorbidities, and their concomitant medications.

2.1. Design Considerations: Disease Registries Vs. Product Registries

Product registries, by definition, focus on patients treated with a particular medical product. To be useful, the registry should record specific information about the products of interest, including route of administration, dose, duration of use, start and stop date, and, ideally, information about whether a generic or branded product was used (and which brand) and/or specific information about the product. Biologic medicines and devices have their own challenges, ideally requiring information about device identifiers, production lots, and batches. Disease registries include information not only on products or procedures of interest, but also on similar patients who receive other treatments, other procedures, or no treatment for the same clinical indications. By characterizing events in the broad population with conditions of interest, disease registries can make a meaningful contribution to understanding adverse event rates by providing large, systematic data collection for target populations of interest. Their generally broad enrollment criteria allow systematic capture on a diverse group of patients, and, provided that they collect information about the potential events of interest, they can be used to provide a background rate of the occurrence of these events in the affected population in the absence of a particular treatment, or in association with relevant treatment modalities for comparison. The utility of this information, of course, depends on these registries' capturing relatively specific and clear information about the events of interest among "typical" patients, and the ability of readers and reviewers to gauge how well the registries cover information about the target population of interest. Generating this kind of real-world data as part of

disease registries can be informative either for the design of subsequent product registries (e.g., to establish appropriate study size estimations) or for the incorporation of new treatments into the data collection as they become available, since the data can provide useful benchmarks against which to assess the importance of any signals. Some would argue that disease registries, rather than specific product registries, are more likely to be successful in systematically collecting interpretable long-term safety data, thereby allowing legitimate comparisons, to the extent possible, across types and generations of drugs, devices, and other interventions.[13]

Consideration should be given during the registry design phase to inclusion/exclusion criteria, appropriate comparator groups, definitions of the exposure and relevant risk window(s), and analysis planning (see Chapter 3). Registries involving products new to the market must be cognizant of selection bias, channeling bias, and unmeasured confounding by indication. Channeling bias occurs when patients prescribed the new product are not comparable to the general disease population. For example, channeling bias occurs when sicker patients receive new treatments because they are nonresponsive to existing treatments; conversely, patients who are doing well on existing treatments are unlikely to be switched to new treatments. Unmeasured confounding can also be introduced by frailty; for example, vaccine effectiveness studies can be misleading if only healthy people get vaccinated.

In some countries, cost constraints imposed by reimbursement status (whether dictated by government agencies or private insurance) mean that new therapies are restricted to narrower populations than indicated by the approved indication. For new devices or procedures, provider learning curves and experience are additional factors that must be considered in analysis planning. Since bias is inherent in observational research, the key is to recognize and control it to the extent possible. In some cases, the potential for bias may be reduced through inclusion/exclusion criteria or other design considerations (e.g., enrollment logs). (See Chapter 3.) In other cases, additional data may be collected and analytic techniques used to help assess bias. (See Chapter 13.) Any recognized potential for bias should be discussed in any publications resulting from the registry.

In some settings, registries are used to collect specific adverse events or events of interest. Once the types of adverse events and/or other special events of interest have been identified, the registry must be designed to collect the data efficiently. Without adequate training of clinical site staff to recognize and report events of interest, the registry will be reduced to haphazard and inconsistent reporting of adverse events.

Upon registry inception, clinicians or other health care professionals who may encounter patients participating in the registry should be educated about what adverse events or other special events of interest should be noted, and how and within what parameters (e.g., time) they should report untoward events that may occur while they are participating in the registry. They also should be reminded about the need to follow up on events that may not obviously be of immediate interest. For example, if a clinician asked a patient how he was feeling and the patient replied that he just returned from the hospital, it would be incumbent on the clinician to obtain additional information to determine whether this might be a reportable event, regardless of whether the patient may have recognized it as such. This is particularly important in registries designed to capture all suspected adverse reactions as opposed to specific adverse events. Such an active role by participants as well as their treating clinicians can contribute to a robust safety database. In addition to identifying events known to be of interest, the systematic collection of

followup data can also capture information regarding risks not previously identified, risks associated with particular subgroups (e.g., pediatric or geriatric patients, patients with liver impairment, fast or slow metabolizers), or differences in event severity or frequency not appreciated during clinical development.

Consideration should also be given to implementation of routine followup of all registry patients for key adverse events, as well as vital status and patient contact and enrollment information at prespecified visits or intervals, to ensure that analyses of the occurrence of adverse events among the registry population are not hampered by extensive missing data. Otherwise, the possibility that patients "lost to followup" may differ from those with repeat visits, with regard to risk of adverse events, cannot be excluded.

It is also important to keep in mind that it may be necessary to revisit the registry design if it becomes apparent that the initial plan will not meet expectations. For example, the original criteria for defining the target population (patients and/or health care providers) may not yield enough patients, such as when a treatment of interest is only slowly coming into use for the intended population.

2.1.1. Health Care Provider- and Patient-Reported Outcomes

Registries and other prospective data collection approaches have the advantage of incorporating both health care provider- and patient-reported data. Although patients and their advocates may spontaneously report postmarketing adverse events to manufacturers (e.g., via inquiries directed to medical information departments) and directly to regulatory bodies, this is relatively uncommon. Furthermore, spontaneous reports received directly from patients that lack health care provider confirmation may fall outside of standard aggregating processes by regulatory bodies. In Europe, there are schemes in some countries to encourage patients to report directly to regulatory authorities; throughout Europe, manufacturers have an obligation to follow up patient reports with their health care provider. However, significant events that are not clinically recognized may be substantially underreported.

In addition, registries may collect health care provider-level data, such as training level, number of patients seen annually, and practice type and locations, that may contribute to understanding differences in event rates and reporting. This, along with the patient-reported data not routinely or consistently captured in the medical record (such as concomitant environmental and lifestyle exposures and adherence to prescribed regimes), differentiates registries from other electronic data sources, and in many cases allows for improved assessment of confounding and ability to assess the potential of a signal internally, prior to further signal evaluation or action.

2.1.2. Effects Observed in a Larger Population Over Time

Registries, including those used to follow former clinical trial participants, are well suited to the identification of effects that can only be observed in a large and diverse population over an extended period of time. They make it possible to follow patients longitudinally, and thereby identify long-term device failures or consequences or delayed drug safety issues or benefits; for example, failures of orthopedic implants increasingly placed in more active, younger patients. Similarly, such long-term followup facilitates evaluation of drug-drug interactions (including interactions with new drugs as they come to market and are utilized) and differences in drug metabolism related to genetic and other patient characteristics.

One of the most consistent risk factors for adverse events is the total number of medications taken by a patient.[14] Polypharmacy is commonplace, especially in the elderly, and health care providers are often

unaware of over-the-counter, herbal, and other complementary (alternative) medications taken by their patients. Registries that collect data directly from patients can seek information about use of these products. In the case of registries used solely by health care practitioners, data collection forms can be designed specifically to request that patients be asked about such use.

When designing a registry for safety, the size of the registry, the enrolled population, and the duration of followup are all critical to ensure applicability of the inferences made from the data. If the background rate of the adverse event in the population of interest is not established and the time period for induction is not well understood, it is extremely difficult to determine an exact meaningful target size or observation period for the registry, and the registry may be too small and have too brief an observation period to detect any, or enough, events of interest to provide a meaningful estimate of the true adverse event rate. In addition, the broad inclusion criteria typical of registries make it likely that subgroups of exposed patients may be identified and analyzed separately. Such stratified analyses may require larger sample sizes to achieve rate estimations with confidence intervals narrow enough to allow meaningful interpretation within strata.

As is also true for clinical trials, which often do not have a sufficient sample size for safety, but rather, for efficacy endpoints, describing safety outcomes from observational studies in statistical terms is not always straightforward. Postmarketing data may or may not confirm event rate estimates seen in clinical trials, and may also identify events not previously observed. During clinical development, risk of events not yet seen but possibly associated with a product class or the product's mechanism of action is often identified as part of ongoing risk assessment, and these events usually continue to be events of interest after approval. An inferential challenge arises when such an event is never observed. The "rule of three" is often cited as a means of interpreting the significance of the fact that a specific event is *not* being observed in a finite population (i.e., that the numerator of its rate of occurrence is zero). Using asymptotic risk estimation, the rule posits that in a large enough study (i.e., >30 patients), if no event occurs, and if the study were repeated over and over again, there can be 95-percent confidence that the event (or events) would not actually occur more often than one in n/3 people, where n is the number of people studied.[15] The rule, originally described by Hanley and Lippman-Hand in 1983, is probably summarized best as a means for "estimating the worst case that is compatible with the observed data."[16] For the purposes of registries, this rule must be carefully applied, since it assumes that reporting of all events occurring in the study population is complete and that the study population is an accurate representation of the intended population. Nonetheless, this rule of thumb provides some guidance regarding registry size and interpretation of results.

2.1.3. Challenges

In planning a registry for safety, it is essential to consider how patients will be identified and recruited in order to understand which types of patients will be included, and equally, if not more importantly, what types of patients will likely *not* be included in the registry. For example, safety registries often seek information about all treated patients, regardless of whether the product is prescribed for an approved indication. While it is conceptually straightforward to design a registry that would include information on all product users, practical challenges include the difficulty of raising awareness about the existence of the registry, the desirability and importance of collecting information on all treated patients, and the challenge of specifying the adverse events and other events of interest without causing undue concern about product safety.

Drawing attention to the registry among health care providers who use the treatments off label is especially challenging, due to competing concerns about being inclusive enough to capture all use (on-label or not) vs. the need, especially if the sponsor of the registry is also a manufacturer, to avoid the appearance of promoting off label use when contacting physicians in specialties known to use the product off label. In addition, diseases targeted for off-label use may be markedly different from indicated uses and may pose different safety issues. In Europe, when there is limited knowledge about the safety of a product prior to its authorization and when a registry is part of a risk management plan, manufacturers may be required, prior to launch of the product, to notify all physicians who may possibly prescribe the product about the existence of a registry (sometimes also called in this context a postauthorization safety study or PASS), including details of how to register patients.

It is more challenging to evaluate the utility of a registry when the entire population at risk has not been included; however, this situation merits careful consideration, since it is far more common than one where a registry captures every single treated patient. Registries organized for research purposes are typically voluntary by design, a situation that does not promote full inclusiveness. Two key questions concern the target population (in terms of representativeness and the potential to generalize the results) and the size of the registry. When considering the target population, it is important to assess (1) whether the patients in the registry are representative of typical patients, and (2) what types of patients may be systematically excluded or not enrolled in the registry. For example, do patients come from a diverse array of health care settings or are they recruited only from tertiary referral hospitals? In the latter case the patients can be expected to be more complicated or have more advanced disease than other patients with a similar diagnosis. Are there competing activities in the target population, such as large registration trials or other observational studies, that may skew participation of sites or patients? Are patients in late stages of the disease or with greater disease severity more likely to participate? (See Chapters 3 and 13 for more information on representativeness.)

The ability to use registries for quantification of risk is highly dependent on understanding the relationship between the enrolled population and the target population. While it is intellectually appealing to dismiss the value of any registry that does not have complete enrollment of all treated patients or a documented approach to sampling the entire population, registries that can demonstrate that the actual population (the population enrolled) is representative of the target population through other means (e.g., by comparison to external data sources) can nevertheless be tremendously informative and may be the only feasible way that data can be collected.

Consider, for example, the National Registry for Myocardial Infarction (NRMI), one of the first cardiac care registries.[17] NRMI was originally intended to obtain information about time to treatment for patients presenting with myocardial infarction to acute care hospitals. The program ultimately resulted in 70 publications (out of more than 500) that provided detailed information on both specific adverse events for specific products and comparative information on safety events. Although this registry was quite large in terms of hospitals and patients, it included neither all MI patients nor all patients using the product for which it described safety information. It was nevertheless considered to be broadly representative of typical MI patients who presented for medical care.

2.1.4. Defining Exposure and Risk Windows

Many patients will enter a registry at various stages in the course of their disease or its medical management. Therefore, it is essential to collect information on the timing of events in relation to the initial diagnosis and in relation to the timing of treatments. It is simplest to collect prespecified clinical data recorded on standardized forms at scheduled assessments, a practice that leads to uniformity within the analysis. However, many registry patients present themselves for data collection on a more naturalistic schedule (i.e., data are collected whenever the patient returns for followup care, whether or not the visit corresponds to a prespecified data collection schedule). The more haphazard schedule is more reflective of "real-world" settings, yet results in nonuniform data collection for all subjects.

Rather than being discarded, these nonuniform data can be analyzed both by categorizing patient visits in terms of time windows of treatment duration (e.g., considering data from all visits occurring within 30 days of first treatment, then within 90 days, 180 days, etc.), and also by using time in terms of patient days/years of treatment. This type of analysis facilitates characterization of the type and rate of occurrence for various adverse events in terms of their induction period and patient time at risk. When the collection of adverse event data is completed through an ongoing active process and is expected to be continued over the long term, periodic analysis and reporting should be structured around specified time points (e.g., annually, semiannually, or quarterly) and may align with the periodic safety update reports. The rigor of prespecified reporting schedules requires periodic assessment of safety and can support systematic identification of delayed effects.

In addition to variability in the timing of followup, consideration must be given to other recognized aspects of product use in the real world; for example, switching of therapies during followup, use of multiple products in combination or in sequence, dose effects, delayed effects, and failures of patient compliance. The current real-world practices for the treatment of many conditions, such as chronic pain and many autoimmune diseases, include either agent rotation schemes or frequent switching until a balance between effectiveness and tolerability is reached—practices that make it difficult to determine exposure-outcome relationships. Switching between biologics may lead to problems with immunogenicity because even products that are clinically the same, as in the case of the erythropoietins, will have different immunogenic potential due to differences in manufacturing processes and starting cell lines. In addition, as with many clinical studies, patient adherence to treatment—or lack thereof—during registry followup is an important potential confounder to consider. Over time, patients may take drug holidays and self-adjust dosages, and these actions should be, but are not always, captured via the data collected in the registry, especially if the interval between followup time points is long or the action is not known by the treating physician. Assessing the temporality of unanticipated events may then be hampered by the inability to fully characterize exposure.

Delayed effects may include late onset immunogenicity, the development of subclinical effects associated with chronic use that are not appreciated until years later, and effects that develop after stopping treatment, related to products with a long half-life or extended retention in the body. An example of this can be seen in the case of bisphosphonates used for bone resorption inhibition in the treatment of osteoporosis, where the product is retained in the bone for at least 10 years after stopping therapy, and there is some evidence that long-term bone turnover suppression puts patients at increased risk of osteonecrosis and nonspinal fractures.[18] In addition, many biologics aimed at immunomodulation carry an increased risk of future malignancy that is not fully appreciated, as do novel therapies directed at

angiogenesis. Although registries are well suited to long-term followup, consideration must be given to how long is long enough to appreciate these effects.

Noncompliance can have a substantial effect on the assessment of adverse events, particularly if dose or cumulative dose effects are suspected. Patient compliance may be affected by expense, complexity of dosing schedule, convenience/mode of administration, and misunderstanding of appropriate administration, and is not fully ascertained by data sources that capture prescriptions rather than actual product use. With products used to treat chronic diseases it is possible to estimate compliance via electronic health records, by first estimating when repeat prescriptions should be issued, and then measuring the observed vs. expected frequency. Although registries may be directly designed to track compliance through patient diaries and other methods of direct reporting, capturing compliance accurately and minimizing recall bias remain challenges.

2.1.5. Special Conditions: Pregnancy Registries

The use of specially designed registries for specific safety monitoring has a long history. For example, pregnancy registries are commonly used to monitor the outcomes of pregnancies during which the mother or father was exposed to certain medical products. The Antiretroviral Pregnancy Registry is an example of a registry that collects information on a broad class of products to determine the risk of teratogenesis.[19] (See Case Examples 46, 47, 48, and 49.) Pregnancy registries provide in-depth information about the safety of one or more products and are particularly useful since, unless the product is used for life-threatening diseases or to treat a pregnancy-related illness, pregnant women are generally excluded from clinical investigations used for product approval. Registries and other observational studies, by virtue of being sustainable over longer periods of time and more amenable to small site-to-patient ratios than registration trials, can facilitate the active surveillance of safety in these populations. In addition, using computerized claims or billing data for pregnancy safety monitoring is hampered by the fact that patients often do not present early in pregnancy, by a lack of relevant data on other exposures (since these are often unrelated to reimbursement), and by difficulty linking maternal and infant records. Therefore, direct prospective data collection currently remains the best source of meaningful safety data related to pregnancy. A challenge for pregnancy registries is to identify and recruit women early enough in pregnancy to obtain reliable information on treatments used during the first trimester, which is a critical time for organogenesis, and to obtain information about early pregnancy loss, since this information is not always volunteered by women. It is also important to obtain information on treatments and other putative exposures before the outcome of the pregnancy is known, to avoid selective recall of exposures by women experiencing bad pregnancy outcomes. For more information, see Chapter 21.

2.1.6. Special Conditions: Orphan Drugs

A product may be designated an orphan drug (or biologic, or medicine in the EU) if it fulfills certain conditions, which include being used for the diagnosis, prevention, or treatment of life-threatening or chronically debilitating conditions affecting a small number of patients. Often these diseases are extremely rare, and dossiers submitted for authorization purposes may have only tens of patients included in clinical trials. Obviously, the safety profile of such products is extremely limited, and followup of patients treated with the products after authorization is likely to be a requirement.

With some orphan drugs, the disease may have been usually fatal before therapy was available. Determining the safety profile of these products is especially difficult, in that the natural history of the

disease when treated is not known, and trying to disentangle the effects of the product from those of the ongoing disease may be particularly problematic. In many of these diseases, the problem may be due to faulty enzymes in metabolic pathways, leading to accumulation of toxic substrates that cause the known manifestations of the disease. Treatment may involve blocking another enzyme or pathway, leading to the accumulation of different substances for which the effects may also not be known but are less immediately toxic. In this situation, with a fatal disease and a first product with proven efficacy, it would not be ethical to randomize patients in a trial vs. placebo for an extended period of time, and so a registry may be the only effective means of obtaining long-term safety data. Registries in these situations may make meaningful contributions to understanding the natural history of the disease and the long-term effects of treatment, sometimes largely by virtue of the fact that most patients can be included and long-term followup obtained for orphan products. For more information, see Chapter 20.

2.1.7. Special Conditions: Controlled Distribution/Performance-Linked Access Systems

Registries in the United States may also be part of risk evaluation and mitigation strategies (REMS), such as restricted distribution systems, referred to as performance-linked access systems (PLAS), which may be used to monitor the safety of marketed products as one of the Elements to Assure Safe Use (ETASU).[20] One of the earliest PLAS was a blood-monitoring program for clozapine implemented in 1990 to prevent agranulocytosis; the program allowed clozapine to be dispensed only if an acceptable blood test had been submitted. Other examples include the STEPS program for thalidomide (System for Thalidomide Education and Prescribing Safety), implemented in 1998 to prevent fetal exposure; the TOUCH controlled distribution for nataluzimab (Tysabri) for patients with multiple sclerosis to detect the occurrence of progressive multifocal leukoencephalopathy (PML); and the iPLEDGE system implemented for isotretinoin in 2006, which tightly links the dispensing of isotretinoin for female patients of childbearing potential to documentation of a negative pregnancy test, to prescriber confirmation that contraceptive counseling has occurred, and to prescriber and patient identification of contraceptive methods chosen.

In many of these programs, access to the product is linked directly to participation in a registry. Therefore, all patients treated with the product should be in the registry because they cannot otherwise obtain access to it. The registry is looking for a known adverse event (such as PML) and collects data specifically related to that adverse event. The registry also collects information on other factors that may raise a patient's individual risk for this adverse event, information that helps provide important clinical context that would not otherwise be available in a systematic fashion on a large population of treated patients.[21]

While PLAS registries are driven by safety concerns, they are primarily focused on prescribing or dispensing controls rather than signal detection. As a result, they utilize very limited data collection forms to minimize burden, and this can limit their utility for certain types of analyses.

In Europe, use of registries for risk minimization activities can be more problematic due to differences in national legislation and enactment of the European Union data protection directive. In some countries it is possible to mandate registration of patients in relation to particular products (e.g., clozapine in the UK and Ireland), but in others other methods must be found. For these reasons, registries are more frequently used on a voluntary basis to monitor safety and capture adverse events, while risk minimization is achieved by controlled distribution with compulsory distribution of educational material, prescribing

algorithms, and treatment initiation forms to anyone likely to prescribe the product. Despite the fact that patient registration is voluntary, high enrollment rates can be achieved, particularly when clinicians recognize that information on the safety profile of the product is limited.[22] Obviously, if a product has a high potential for off-label use, patients enrolled in a registry may not be generalizable to all those treated with the product, but this can be factored into data analysis and interpretation. A voluntary registry coupled with controlled distribution may, in fact, be reasonably representative, since off-label use may be severely limited by difficulties obtaining the product.

2.1.8. Special Conditions: Medical Devices

Medical devices pose different analytic and data challenges from drugs. On the one hand, it is much more straightforward to identify when a device is implanted and explanted if those records can be obtained; however, since not all medical devices are covered by medical insurance, it can be more difficult to identify all the appropriate practitioners and locate all the records. Medical devices that can be attached and detached by the consumer, such as hearing aids, are very difficult to study in that, much like products used on an as-needed basis, special procedures are required to document their use; these procedures are costly and intrusive, and therefore rarely used. Additionally, the lack of unique device identifiers has posed a challenge for safety surveillance of devices. Recently, the FDA proposed a new system that will establish a unique identifier for most medical devices, with the goals of supporting more accurate reporting and analyzing of medical device adverse event reports (see Chapter 23).

Despite these challenges, the safety of medical devices is very important due to their widespread use; of particular concern are long-term indwelling devices, for which recall in the event of a malfunctioning product is inherently complicated. For example, in the late 1970s/early 1980s, when a particular type of Björk-Shiley prosthetic heart valve was found to be defective and prone to fracture, leading to sudden cardiac death in the majority of cases, detailed studies of explanted devices, patient factors, and manufacturing procedures led to important information that was used to guide decisionmaking about which devices should be explanted.[23,24] Identification of the characteristics of valves at high risk of failure was very important due to the perioperative mortality risk from explanting a heart valve regardless of its potential to fail. This same logic applies to many other medical devices that are implanted and intended for long-term use. Some of the challenges relating to studying medical devices have to do with being able to characterize and evaluate the skill of the "operator," or the medical professional who inserts or implants the device. These operator characteristics may be as, or more, important in terms of understanding risk than the characteristics of the medical devices themselves.[25] For more information, see Chapter 23.

3. Registries Designed for Purposes Other Than Safety

Registries may be designed to fulfill any number of other purposes, including examining comparative effectiveness, studying the natural history of a disease, providing evidence in support or national coverage decisions, or documenting quality improvement efforts. Although these registries may gather data on adverse events and report those data (to regulatory authorities, manufacturers or others), not all data may necessarily be reported *through* the registry. Thus, the registry may not record all events, which would result in an imprecise, and possibly inaccurate, estimation of the true risk in the exposed population(s). A strength of comparative effectiveness registries, however, lies in the systematic collection of data for both the product of interest and concomitant, internal controls.

As an example of the limitations of assessing safety events in registries not designed for safety, a registry may be sponsored by a payer to collect data on every person receiving a certain medication. The purpose of the registry may be to assess prescribing practices and determine which patients are most likely to receive this product. The registry may also contain useful data on events experienced by patients exposed to the product, but may not be considered a comprehensive collection of safety data, or may provide information regarding a known risk or outcome rather than generating data that could identify a previously unappreciated event. Alternatively, a registry may be designed to study the effectiveness of a new product among a population subset, such as the elderly. The registry may be powered to analyze certain outcomes, such as rehospitalizations for a condition or quality of life, but may not be specifically of sufficient sample size to reliably assess overall safety in this population.

It is more challenging to accurately and precisely detect adverse events of interest when a registry has not been designed for a specific safety purpose. In this situation, the registry must collect a wide range of data from patients to try to catch any possible events, or be adapted later should safety become a primary objective. Some events may be missed because the registry did not anticipate them and did not solicit data to identify them. Also, much the same as for registries designed specifically to detect adverse events, some events may be so rare that they do not occur in the population enrolled in the registry or do not occur during the registry followup period. In these circumstances, registries can be designed to provide useful data on some of the events that may occur in the exposed population. Such data should not be considered complete or reliable for determining event rates, but, when the data are combined with safety data from other sources, trends or signals may become apparent within the dataset.

4. Ad Hoc Data Pooling

One way to capitalize on data that, because they were collected for another purpose, may be insufficient for meaningful stand-alone analysis and interpretation due to study size or lack of comparators, is to pool the data with other similar data. As with any pooling of disparate data, the use of appropriate statistical techniques and the creation of a core dataset for analysis are critically important, and are highly dependent on consistency in coding of treatments and events and in case identification.

It is essential to have an understanding of how every dataset that will be used in a pooled analysis was created. For example, what is recorded in administrative health insurance claims depends largely on what benefits are covered and how medications are dispensed. Noncovered items generally are not recorded. For example, mental health services are often contracted for under separate coverage (so-called "carve-outs") and not covered under traditional health insurance coverage; thus, the mental health consultations are not likely to be included in administrative databases derived from billing claims data. Also, some injectable medications (e.g., certain antibiotics) may be administered in the physician's office and thus would not be recorded through commonly used pharmacy reporting systems that are based on filling and refilling prescriptions. The absence of information may lead to false conclusions about safety issues. Also, adverse event data coded using the same coding dictionary (e.g., MedDRA) may still be plagued by inconsistency in the application of coding guidelines and standards. Recoding of verbatim event reports may be required, if feasible, prior to analysis. Depending upon the purpose for which the data were collected, data on the treatments of interest are not always recorded, or are not recorded with the specificity needed to understand risk (e.g., branded vs. generic, dosage, route of administration, batch).

Another consideration is differential followup, including the duration and vigor of followup in the registries to be pooled. Particular care is needed when combining datasets from different European countries, since differences in medical practice and reimbursement may mean that superficially similar data may actually represent different subgroups of an overall disease population. Similar caution is also advisable when combining information from disparate health systems within a single country, as some treatments of interest may be noncovered benefits in some systems and consequently not recorded in that health system's records. An alternative to pooling data is to conduct meta-analyses of various studies using appropriate statistical and epidemiologic methods.

While the types of registries described above may not be individually of sufficient sample size to detect safety issues, combining data from registries for other purposes could significantly enhance the ability to identify and analyze safety signals across broader populations. Core datasets for adverse events have been suggested for electronic health records systems and as part of national surveillance mechanisms (e.g., through distributed research networks). In such a network, each participating registry or data source collects a standardized core dataset from which results can be aggregated to address specific surveillance questions. For example, there is significant national interest in understanding the long-term outcomes of orthopedic joint implants. Currently, there are several prominent registries in the United States with varying numbers of types of patients and types of implants. Many of these registries collect data for quality improvement purposes, but have sufficient data elements to potentially report on adverse events. However, only by aggregating common datasets across many of these registries can a broadly representative population be evaluated and enough data accrued to understand the safety profile of specific types of devices in particular populations.

As described above, while not every registry is designed to evaluate safety, even registries designed for other purposes might contribute to aggregate information about potential harm from health care products or services. Yet many registries, especially disease registries, are conducted by nonregulated entities such as provider associations, academic institutions, and nonprofit research groups, whose role in adverse event reporting is unclear. Furthermore, sample sizes needed to understand safety signals are generally much larger than those needed to achieve useful information on quality of care or the natural history of certain diseases, and the safety analyses can require a high degree of statistical sophistication. Enrolling additional patients or committing additional resources for specialized analyses in order to achieve a general societal benefit through safety reporting is not feasible for most registries when the primary purpose is not safety. However, encouraging registries to participate in aggregation of data when such participation is at minimal cost and enhances the common good may be both reasonable and appropriate.

Many efforts are underway to improve the feasibility of broader safety reporting from both registries and electronic health records that serve other purposes. These efforts include recommending standardized core datasets for safety to enhance the aggregation of information in distributed networks, and making registries interoperable with facilitated safety reporting mechanisms or other registries designed for safety.[26] As facilitated reporting methodologies become more common and easier for registries to implement, there will be fewer reasons for nonparticipation. In addition, linkage of population-based registries, such as the Surveillance, Epidemiology and End Results (SEER) cancer registry program, with other data sources, such as Medicare, have proven invaluable for evaluating safety and other outcomes.

5. Signal Detection in Registries and Observational Studies

Although subject to debate, according to the World Health Organization (WHO) definition, a safety signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."[27] Hauben and Aronson (2009) define a signal as "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions."[28] The authors further posit that signals, following assessment, could subsequently be categorized as indeterminate, verified, or refuted.

Additional attempts at defining or describing a safety signal for purposes of guiding product sponsors, regulators, and other researchers have come from various sources, including the Council for International Organizations of Medical Sciences (CIOMS), the FDA, and the UK's Medical and Healthcare products Regulatory Agency (MHRA). Nelson and colleagues recently provided FDA with a comprehensive evaluation of signal detection methods for use in postmarketing surveillance, and included a discussion of "conventional Phase IV observational safety studies," which would encompass registries, as part of a multipronged approach to surveillance.[29] They noted that despite a focus on automated health care data sources, such as large health care claims databases, for primary surveillance and as the basis for FDA's Sentinel Network, the need for more detailed data regarding exposure and outcome measurement, as well as collection of relevant confounder data, will require that prospective observation studies be conducted to address prespecified safety-related hypotheses.

Establishing a threshold of effect size and robustness of data that would justify action, such as initiation of additional studies, FDA action, or changes in payer coverage, remains an important question and is unlikely to be uniformly applicable to all products and situations. A report was issued in 2010 from the CIOMS Working Group VIII, whose main goal is to harmonize the development, application, and interpretation of signal detection methods for use with drugs, vaccines, and biologics and to provide practical advice.[30]

Once a signal that warrants further evaluation is identified, it is typically assessed based on the strength of the association between exposure and the event; biological plausibility; any evidence provided by dechallenge and rechallenge; the existence of experimental or animal models; and the nature, consistency, and quality of the data source.[31] Signals may present themselves as idiosyncratic events affecting a subset of the exposed population who are somehow susceptible, events related to the pharmacological action of the drug, or increased frequency of events normally occurring in the population (such as in the example of cardiovascular events and rofecoxib). Signals may involve the identification of novel risks, or new (or more refined) information regarding previously identified risks. If an event does appear to be product related, further inquiry is required to examine whether the occurrence appears to be related to a specific treatment, a combination or sequence of treatments, or a particular dosage and/or duration of use. Events with long induction periods are particularly challenging for the ascription of a causal relationship, since there are likely to be many intervening factors, or confounders, that could account for the apparent signal.

The constant challenge is to separate a potential safety signal from the "noise," or, in other words, to detect meaningful trends and to have a basis for evaluating whether the signal is something common to

people who have the underlying condition for which treatment is being administered, or whether it appears to be causally related to use of a particular product. All methods currently used for signal detection have their limitations. Attempts to use quantitative, and in some cases, automated signal detection methods as part of pharmacovigilance, including data mining using Bayesian algorithms or other disproportionality analyses, are hampered by confounders and other biases inherent to spontaneously reported data.[32,33] Other methodologies also attempt to identify trends over time and include potential patterns associated with other patient characteristics, such as concomitant drug exposures.

These methods of automated signal detection lack clinical context and only draw attention to deviations from independence between product exposure and events. No conclusions regarding causality can be drawn without a further qualitative and quantitative assessment of extrinsic factors (e.g., an artificial spike in reporting due to media attention) and potential confounders; in some cases, even with quantitative and qualitative assessments, the data may be insufficient to establish causality. Depending on the original data source, it may be impossible to address these issues within the database itself and either abstracted medical record data or prospective data collection may be required to gather reliable data. The long-term followup and longitudinal data generated by many registries merits particular methodological considerations, including how often to perform testing, what threshold is meaningful for a given event, and whether that threshold changes over time.

While some registries can serve as sources of initial safety signaling or hypothesis generation, they may also be utilized for further investigation of a signal generated from surveillance and quantitative analysis. As an example, existing data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), sponsored by the Swedish Health Authorities, was used to look at long-term outcomes related to bare-metal and drug-eluting stents, once it became clear through FDA-designed and other registries in the postmarket setting that off-label use was very common and that the risk of restenosis and other long-term outcomes in the real-world patient population was not fully understood. Due to the existence of comprehensive national population registries in Sweden, researchers were able to reliably combine SCAAR data, which captured unselected, consecutive angiography and percutaneous coronary intervention procedure data, with vital status and hospitalization data, to examine fatality rates and cardiac events on a population level.[34] This use of procedure and national registries provides an example of how a registry that included a well-defined population allowed for safety assessments coincident with comparative effectiveness.

6. Potential Obligations for Registry Developers in Reporting Safety Issues

In considering what actual and potential obligations there are, or may be, for registries in product safety assessment, it is useful to separate the issues into several parts. First, there are two key questions that can be asked for each registry: (1) What is the role of registries not designed for safety purposes with respect to the search for adverse events? and (2) What are the obligations, especially for those registries not sponsored by regulated manufacturers, to further investigate and report these events when found? As discussed above, registries can be classified by whether or not they were designed for a safety purpose, and also by whether or not they have specified regulatory obligations for reporting. Beyond these distinctions, several factors need to be considered, including the ethical obligations of the registry developer, the technical limitations of the signal detection, and resource constraints.

Registries designed for safety assessment purposes should have a clear and deliberate plan in place, not only for detecting the signal of interest, but for handling unanticipated events and reporting them to appropriate authorities. Only in the case of registries supported by the regulated industries are rules for reporting drug or device adverse events explicit. Therefore, it would be helpful if other registries would also formulate plans that ensure that appropriate information will reach the right stakeholders, either through reporting to the manufacturer or directly to the regulator, in a timely manner similar to those required by the regulated industries. There should not be two different standards for reporting information intended to safeguard the health and well-being of all.

Registries that are not designed specifically for safety assessment purposes, particularly those that are not sponsored by a manufacturer, raise more complex issues. While researchers have an obligation to the patients enrolled in any research activity to alert them should information regarding potential safety issues become known, it is less clear how far this obligation extends. In the UK, the General Medical Council includes in its advice on "Good Medical Practice" the requirement to "report suspected adverse drug reactions in accordance with the relevant reporting scheme."[35] It is therefore clear that in the UK contributing to the safety profile of a medicine is regarded as part of the duties of a medical practitioner. During its review of research registries, an institutional review board (IRB) (U.S.) or ethics committee (EC, in Canada or the European Union) may specify the creation of an explicit incidental findings plan prior to approval. Such a plan is often part of studies producing or compiling nonclinical imaging and genetic data. In addition, some investigators will have an obligation to report to an IRB or EC any unanticipated problems involving risks to subjects or others under the regulations on human research protections. In turn, IRBs and ECs have an obligation to report such incidents to relevant authorities.

At a minimum, all registries should ensure that standard reporting mechanisms for adverse event information are described in the registry's procedural documents. These mechanisms should also be explained to investigators and, where feasible, their reporting efforts should be facilitated. For example, all registries in the United States can make available to registry participants access to the MedWatch forms[36] and train them in the appropriate use of these forms to report spontaneous events. As described in Section 4 above, in the near future it should be possible for registries that collect data electronically to actually facilitate the reporting of adverse events by linking with facilitated safety reporting mechanisms. This mechanism is attractive because it reduces the work of the investigator in generating the report and ensures that the report will go to a surveillance program prepared to investigate and manage both events and potential safety signals.

Obligations beyond facilitation are less clear. Furthermore, there are both technical and resource obstacles to thoroughly investigating potential signals, and risks that inaccurate and potentially injurious information will be generated. For example, publicizing product safety issues can result in some patients discontinuing use of potentially life-saving products regardless of the strength of the scientific evidence. As described earlier, registries designed for safety assessment should ideally have both adequate sample size and signal evaluation expertise in order to assess safety issues. Registries not designed for safety purposes may not have enough patients or statistical signal detection expertise to investigate potential signals, or may not have the financial resources to devote to unplanned analyses and investigations. It would seem that, at a minimum, registries not designed for safety purposes should use facilitated reporting (via training, providing forms, etc.) of individual events through standard channels to meet their ethical obligations, and that they should check with any institutions with which they are affiliated to

determine whether they are subject to additional reporting requirements. However, should a registry identify potential signals through its own analyses, obligations arise.

While registries that are approved by IRBs report safety issues to those IRBs, incidental analytic findings, which may represent true or false signals, may need more definition and should best be further investigated and reported for the public good. One approach would be to report summary information to the relevant regulatory authority for further evaluation. To avoid doubt, registry developers should consider these issues carefully during the planning phase of a registry, and should explicitly define their practices and procedures for adverse event detection and reporting, their planned analyses of adverse events, and how incidental analytic findings will be managed. Such a plan should lay out the extent to which registry owners will analyze their data for adverse events, the timing of such analyses, what types of unanticipated issues will be investigated internally, what thresholds would merit action, and when information will be provided to regulators or other defined government entities, depending on the nature of the safety issue.

7. Summary

The ongoing challenge, in the use both of existing data and of prospective data collection efforts such as registries, is to cast a wide enough net to capture not only rare events, but also more common events and events that are not anticipated (i.e., not part of a preapproval or postapproval potential risk assessment). In some cases, existing registries may add additional data collection to address questions regarding possible adverse events that arise after registry initiation. In addition, it must be considered that all observational data sources are only as strong as their ability to measure and control for potential biases, including confounding and misclassification.

Large registries, linkage and distributed network schemes, and sentinel surveillance are all tools being actively developed to create an integrated approach to medical product safety and, specifically, to signal detection and verification.

In contributing to the evidence hierarchy surrounding the generation of signals for detection and confirmation of potential adverse events, registries are likely to make their strongest contributions through: detection of novel adverse events associated with product use as reported by treating physicians, which, in turn, constitutes a signal necessitating further study; gathering information about pregnant women and other hard-to-study subpopulations of product users; linking with additional data sources such as the Medicare-SEER data linkage, thereby broadening the range of questions that can be addressed beyond the constraints of data collected for a registry; and confirming or validating signals generated in other data, such as from automated signal generation in large claims databases. Ideally, a clear and prospective understanding among stakeholders is needed regarding if and under what circumstances signal monitoring within registries is appropriate; the timing or periodicity of any such analyses; what should be done with the information once it is identified, and what, if any, are the ethical obligations to collect, analyze, and report safety information if doing so is not a planned objective of the registry, and if the registry sponsor is not directly required to conduct such reporting by regulation.

Thoughtfully designed registries can play important roles in these newly emerging strategies to utilize multiple available data sources to generate and strengthen hypotheses in product safety. However, as with all data sources, it is important to assess the effects of registry design, the type of data, reason for the data collection, how the data were collected, and the generalizability to the target population, in order to assess

the strengths, weaknesses, and validity of the results provided and their contribution to the knowledge of the safety profile of the medicine or device under study.

References for Chapter 19

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Case Examples for Chapter 19

Case Example 41. Using a Registry To Assess Long-Term Product Safety

Description	The British Society for Rheumatology Biologics Register (BSRBR) is a prospective observational study conducted to monitor the routine clinical use and long-term safety of biologics in patients with severe rheumatoid arthritis and other rheumatic conditions. The United Kingdom-wide national project was launched after the introduction of the first tumor necrosis factors (TNF) alpha inhibitors.
Sponsor	The British Society for Rheumatology (BSR) commissioned the registry, which receives restricted funding from Abbott Laboratories, Biovitrum, Schering Plough, Roche, and Wyeth Pharmaceuticals. The registry is managed by the BSR and the University of Manchester.
Year Started	2001
Year Ended	Ongoing
No. of Sites	All consultant rheumatologists in the United Kingdom who have prescribed anti-TNF therapy participate.
No. of Patients	More than 17,000

Challenge

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterized by joint damage, pain, and disability. Among the pharmacologic treatments, nonbiologic disease-modifying antirheumatic drugs (DMARDs) are considered the first-line treatment. Novel biologic therapies represent a new class of agents that prevent inflammation and have demonstrated efficacy in RA patients. The most commonly used biologics are tumor necrosis factors (TNF)* inhibitors (etanercept, infliximab, and adalimumab). However, results from clinical trials and pharmacovigilance studies have raised potential safety concerns, and limited long-term data on these therapies are available. Of particular concern has been an increase of tuberculosis observed in patients treated with anti-TNF therapy.

Proposed Solution

A prospective observational registry was launched in 2001 to monitor the safety of new biologic treatments. The registry collects data on response to treatment and potential adverse events every six months, and patients are followed for the life of the registry. Over 4,000 patients are enrolled for each of the anti-TNF agents (etanercept, infliximab, and adalimumab), and the registry represents approximately 80 percent of RA patients treated with these biologics in the United Kingdom. In addition to patients receiving anti-TNF* therapy, the registry has enrolled a control cohort of patients receiving nonbiologic DMARDs.

Results

Data from the registry were analyzed to determine whether an increased risk of tuberculosis existed in RA patients treated with anti-TNF therapy (Dixon et al., 2010). In more than 13,000 RA patients included up to April 2008, 40 cases of tuberculosis were observed in the anti-TNF cohort and no cases in the

DMARD group. A differential risk was reported among the three anti-TNF agents, with the lowest risk observed in the etanercept group. The incidence rates were 144, 136, and 39 cases per 100,000 person-years for adalimumab, infliximab, and etanercept, respectively. In addition, the incidence rate ratio, median time to events, and influence of ethnicity were evaluated.

Key Point

As novel drugs and treatments are developed and licensed, registries may be useful tools for collecting long-term data to assess known and emerging safety concerns.

For More Information

Dixon WG, Hyrich KL, Watson KD. et al. Drugspecific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Annal Rheum Dis. 2010;69(3):522–8.

Zink A, Askling J, Dixon WG. et al. European biological registers: methodology, selected results and perspectives. Annal Rheum Dis. 2009;68:1240–6.

Case Example 42. Using a Registry To Monitor Long-Term Product Safety

Description	SINCERE™ (Safety in Idiopathic arthritis: NSAIDs and Celebrex Evaluation Registry) is a multi-center registry designed to monitor the long-term safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with juvenile idiopathic arthritis (JIA). The registry included patients ages 2 to 17 and collects demographic, developmental, clinical, and safety data. The followup period was at least 2 years, and as long as 4 years for some patients.
Sponsor	Pfizer, Inc.
Year Started	2009
Year Ended	2012 (terminated early)
No. of Sites	16 sites in the United States
No. of Patients	Planned enrollment of 200 patients on celecoxib and 200 patients on other NSAIDs. Actual enrollment of 219 on other NSAIDs, 55 on celecoxib, for 274 total

Challenge

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for more than 30 years to relieve pain and inflammation in juvenile idiopathic arthritis (JIA), and it is estimated that 80 to 90 percent of JIA patients will use an NSAID at some point. However, little is known about the long-term safety of chronic use of NSAIDs in children with JIA. This question is particularly important as many children with JIA will continue to use NSAIDs well into adulthood. Due to the rarity of JIA and the special ethical issues surrounding children's participation in experimental studies, randomized controlled trials of NSAIDs in JIA are considerably smaller and of shorter duration than adult arthritis trials; the pivotal trial for celecoxib in JIA, one of the largest NSAID JIA studies, had 100 patient-years of exposure. In addition,

randomized trials may not be generalizable to typical JIA populations. Lastly, it is unclear if the emerging safety concerns in adult NSAID and celecoxib users translate to children, who are much less likely to develop serious cardiovascular thromboembolic events or gastrointestinal bleeding events.

The development of a long-term observational study was necessary to address these knowledge gaps, fulfill a postmarketing safety commitment, and respond to concerns of regulators, patients, physicians, and the sponsor.

Proposed Solution

This multicenter registry was designed to gather long-term safety data on NSAIDs' use in children with JIA, and intended to enroll a quasi-inception cohort of patients aged 2 to 17 years and >10 kg who were prescribed (not more than 6 months prior) either celecoxib (n = 200) or other NSAIDs (n = 200). Pediatric rheumatologists from 16 sites in the United States entered data quarterly for the first 12 months and twice annually thereafter. The registry intended to follow all patients for at least 2 years and as long as 4 years, as all patients were encouraged to remain in the registry until the last patient completed the minimum followup. Concomitant medications and treatment switches were permitted, and patients were followed for residual effects even if NSAID treatment was discontinued.

Targeted events of interest (i.e., cardiovascular, gastrointestinal, and hypertension) and general safety serious and nonserious adverse events (AEs) were collected in a systematic manner. The Common Terminology Criteria for Adverse Events (CTCAE ver 3.0) criteria were used to both code and grade all AEs to minimize variability across physicians. In designing the registry, particular attention was paid to collecting potential covariates relevant to confounding by indication, given the expected differential prescribing between celecoxib and other NSAIDs. The analyses summarized the incidence of the targeted events and AEs in general, and exploratory analyses may further characterize AE rates by other clinical and demographic factors.

Results

The registry was terminated early due to low patient recruitment, despite multiple attempts to improve site and patient enrollment. The primary issue identified as a barrier to enrollment was that the treatment paradigm had changed since celecoxib was first approved: with the advent and increasing use of biologic therapies, NSAIDs were no longer being used long-term in JIA very often. As a result, the objective of the study, to assess the long-term safety of celecoxib as used for JIA, could not be met. This change in treatment paradigm, coupled with safety information from the registry and other sources that indicated no new signals nor change to the benefit-risk profile of celecoxib as used in children with JIA, allowed the FDA to release the sponsor from the commitment and terminate the study early due to futility. The registry nevertheless provided over 410 patient-years of observation in this cohort of NSAID and celecoxib users, providing additional safety data on these drugs as used for JIA in routine clinical practice; no new safety issues were identified. This information may facilitate appropriate therapeutic decision-making for doctors and patients.

Key Point

Registries may be useful tools for examining long-term product safety, particularly in populations such as children that are difficult to study in randomized controlled trials. Changes in the treatment paradigm of a disease may affect the utility and feasibility of a long-term product safety registry.

For More Information

Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011 Apr;63(4):465-82.

Chapter 20. Rare Disease Registries

1. Introduction

There is no single, unifying definition of a rare disease. Rare diseases are defined, from a regulatory and policy perspective, as any condition or disease affecting fewer than 200,000 individuals in the United States, or alternatively, determined to be of low prevalence (less than 5 individuals per 10,000) in the European Union.[1,2] In the United States, the Orphan Drug Act (P.L. 97-414) was adopted in 1983 in an effort to encourage activities by industry (and to a lesser extent other funding and research bodies) through tax incentives, market exclusivity, user fee exemptions and other incentives to target development of therapies for rare diseases.[3] This legislation, as well as other regulations and similar international initiatives, resulted in a marked increase in rare disease research funding and development efforts for related drugs and biologics. Success of these compounds in coming to market, however, has been hampered by an incomplete understanding of the underlying disease mechanisms and relevant clinical endpoints, as well as limitations associated with identifying a large enough sample of comparable patients for clinical trials.

The scarcity of relevant knowledge and experience with most rare diseases creates a unique need for cooperation and infrastructure. Support is needed for research initiatives that aim to better understand the distribution and determinants of these diseases and to develop new therapies and other interventions. Innovations in genetics, molecular and computational biology, and other technological advances in basic research are rapidly evolving; however, translating this progress into clinic research and securing governmental or private funding in early stages remains challenging. Some of these challenges can be addressed efficiently through a systematic collection of clinical, genetic, and biologic data in the form of longitudinal patient registries and other coordinated data sources.

The use of observational data methods, including prospective long-term patient registries, is a critical tool in building a broad and comprehensive knowledge base for these often heterogeneous diseases. Important data include the prevalence and distribution of these diseases and key patient, familial, and disease characteristics, including the natural history of the disease. Although many of the basic concepts around registry planning, design, and implementation are directly applicable these disease registries, rare diseases pose some unique challenges. The range of stakeholders for rare diseases is inherently different, which has a direct effect on implementation, governance, funding, communication and as well as their level of interest and willingness to participate in the study of rare diseases. Clinicians with relevant expertise and direct exposure to managing these patients are limited, necessitating a broad outreach to identify and recruit enough patients to understand the epidemiology and natural history of the disease. In addition, because of the knowledge gaps that exist, the scope and objectives of rare disease registries are often more broad than in a typical disease registry. The absence of standards of care or treatment guidelines in many cases, the common use of experimental and adjunctive therapies, and the incomplete understanding of how these conditions should be monitored in the absence of established or widely accessible biomarkers provide opportunities for rare disease registries to set the agenda for disease research. Since amassing a sizable population from which any patterns of rare diseases can be discerned is more difficult, novel approaches are often required to both define rare diseases and their relevant outcomes (in other words, scientifically validated and accepted criteria may not exist). Lastly, patient advocacy and support

groups are smaller for these often less well-known diseases and may play different roles than in a more traditional disease registry.

This chapter provides an overview of the development of patient registries for rare diseases and the key stakeholders and challenges that are specific to these registries. Case Examples 43, 44, and 45 offer some descriptions of rare disease registries. The reader is directed to other chapters regarding relevant good registry practices.

2. Genesis of a Rare Disease Registry

2.1. Rare Disease Registry Objectives and Scope

Rare disease registries are initiated by many organizations, such as patients and their families, patient advocacy groups, clinicians, national health systems, and biopharmaceutical product manufacturers, for many reasons. Often, rare disease patient registries have grown organically. In rare diseases where patients are few, research agendas do not exist, standard case guidelines are absent, and patient communities have not yet formed, patient registries are an intuitive first step for stakeholders trying to understand the number of people affected, their geographical distribution, and the basic demographic and clinical characteristics of the disease. The scope of these registries may evolve over time, maturing from an outreach/community-building effort or a means for a basic understanding of patient and disease characteristics, to a supportive mechanism for research funding and attracting healthcare providers. As with all registries, a single rare disease registry need not fulfill all goals for all potential stakeholders. Ideally, however, a well-designed registry provides an infrastructure that can support different needs in an efficient way and eliminate barriers to scientific progress.

It should be noted that rare disease registries include not only diseases that are inherently rare, but also common diseases that are rare in specific populations, especially those defined by demographics. Thus, plaque psoriasis – common among adults – is rare in children, and breast cancer – common among women – is rare among men. While some of the objectives specific to rare disease registries will apply (e.g., patient identification and recruitment), others may not (e.g., disease classification, measuring disease-specific outcomes).

Registries can be developed to serve multiple purposes. The design of the registry depends upon the maturity of the research plan around the disease, the availability and duration of funding, and, to some extent, the number of patients affected. For rare diseases, the perception of relative research importance of research often correlates with the number of patients affected or empowered disease advocates.

The specific objectives of rare disease registries typically cluster into the following categories:

1. **To connect affected patients, families, and clinicians**

Patients and families of affected individuals are often interested in knowing about others who share their disease. Many rare diseases have a genetic basis. However, even if multiple family members are affected with the condition, the motivation to be connected to others may be quite strong, driven by their personal desire to know more about the condition, its natural history, alternative coping mechanisms and treatment options, and the diversity of clinical courses and outcomes. The need to connect is enhanced if the patient

or family has difficulty in finding an expert to provide advice or the doctor or genetic counselor points out how little is known about the rare condition.

Registry meetings provide an opportunity to talk and to share personal experiences. These meeting may include lectures and discussion among patients and families and with experts in medicine, dentistry, nursing, sociology, and many other fields. The advent of social media has increased patient involvement in these types of activities by encouraging patient-to-patient dialogue and assisting with recruitment for research and support. Patients and families often want to connect to advocate support of patients' services and financial support for patient care and research.

Similarly, physicians and other clinicians may want to connect with other clinicians to learn more about the disease and possible treatment options. Most clinicians have not seen a wide spectrum of rare diseases, and little information on some diseases may be available in the literature. Registries may offer a connection to essential information and to experts in the disease area to assist healthcare providers with advising and counseling patients.

2. To learn the natural history, evolution, risk, and outcomes of specific diseases

Stakeholders often initiate registries to learn the natural history of a rare disease. Typically, rare diseases are described in a general way based on their symptoms at the time of diagnosis. With refinement in diagnostic techniques, including genetic, biochemical, and physiological testing, classical disease descriptions are broadened, and diseases are better described in terms of the range and likelihood of specific outcomes. Unlike more common diseases where criteria for classification will often evolve, such evolution may not be possible for rare diseases, but the acceptance of some general criteria that derive from these studies will inform and help subsequent research. As general and specific therapies emerge, the natural history often changes and the "classical description" may no longer apply. With better therapies for treatment and supportive care, new complications may also be recognized. For treatments that extend life expectancy, what is known about the trajectory of disease can change drastically. A disease registry incorporating patients with rare diseases from many centers allows for gathering stronger and more generalizable safety, diagnostic, and prognostic information.

For industry, natural history of disease registries are often developed to better understand the burden of disease, elements of disease progression, disease genotypic and phenotypic heterogeneity, and potential endpoints (or surrogate endpoints) that may be utilized in therapeutic clinical development. Increasingly, these types of disease registries are also used to understand patient and caregiver quality of life and the economic consequences of these diseases, as well as to understand the background risk of specific outcomes (i.e., provide a reference population) that usually cannot be found or inferred from other sources of data when the disease is rare.

3. To support research on genetic, molecular, and physiological basis of rare diseases

Research on features of disease, both clinical and basic, is a common objective of a registry. Clinical research depends on having a representative population for determining the timing and frequency of natural events and complications, such as development of autoimmune complications, unusual infections, and related or unrelated malignancies. For this reason, rare disease registries benefit from a comprehensive database that is sufficient to address critical clinical questions, while at the same time not

being so all-inclusive that the data cannot be acquired and maintained with reasonable effort on the part of the registry team.

Patients, researchers, and clinicians share interests in understanding diseases at the genetic, molecular, and cellular level. Such studies usually require a bio-repository of materials, including tissue (fresh and frozen), DNA, RNA, cellular proteins, and bodily fluids for research. Creating a meaningful repository for the study of rare diseases requires collection of materials from a sufficient population to permit generalization about the fundamental features and diversity of the disease at the genetic, molecular, and cellular level. A registry is an important complement to any bio-repository; similarly, bio-repositories are far stronger if they are closely linked to a registry that contains relevant longitudinal clinical or phenotype data. In cases where multiple small or regional registries exist for a specific condition, a centralized bio-repository can serve as a common link and research resource. Valid interpretation of biosample research depends on understanding the clinical features of the patients and the heterogeneity of the disease in the study population. In addition, the existence of parallel relevant longitudinal clinical data allows for assessment of genetic and environmental disease modifiers.

4. To establish a patient base for evaluating drugs, medical devices, and orphan products

Stakeholders are vitally interested in developing drugs, devices and other therapies for rare diseases, and many rare disease registries have been developed to support the drug development process. Patient registries for rare diseases may emerge from suggestion, pressure, or advocacy of affected patients and/or families. Direct influence can be seen when patients and their caregivers decide they want a registry, raise the funds, and push for its creation. Indirect influence can be seen when patients or special interest groups drive government to make research on that disease a priority. Researchers and industry recognize that a population of patients is essential for clinical testing, and industry may provide rare disease groups with support to begin or expand a fledgling registry so that ultimately a potentially useful drug or device can be tested in the disease population.

Often, developing a treatment for a rare disease will provide information about pathophysiology that informs treatment development of a related disease. If the rare disease is serious with few or no treatment options, regulators may relax some of the requirements for drug registration (as is indicated by the requirements for orphan drug development).

2.2. Rare Disease Registry Stakeholders

Any registry endeavor has a number of stakeholders, often with both convergent and divergent agendas. Stakeholders may include patient advocacy groups (often multiple), regulatory agencies (especially if the registry is being developed to support future drug development and approval or to fulfill post-marketing commitments or requirements), clinicians, scientists, industry, payers, and the individuals and families affected by the disease. Collaboration between stakeholder groups has been critical to the progress made in research and product development, the adoption of important public policy changes in the United States and worldwide, and the promotion of patient access to treatments as they become available.[4] Table 25 describes potential registry stakeholders and the roles that they may play in registries.

The importance of patient registries in rare diseases and the need to support many organizations has also brought umbrella patient organizations (e.g., NORD, the Genetic Alliance, EURORDIS) in as stakeholders, as these groups are charged with advising and supporting the development of registries. As

the number of registries increases along with the number of commercial companies to develop and host them, these umbrella organizations are becoming brokers for services and are motivated to identify standards and shared efficiencies to support patient registries for the thousands of rare disorders that need them. In addition, the proliferation of patient registries for rare diseases brings standards development organizations and standards interests into the fold, as the need for standards that can facilitate data sharing (i.e., common data elements) between patient registries and other aspects of healthcare and clinical research has become evident. More broadly, the vision of patient registries that can share data between both electronic health records and personal health records as well as with clinical research or national public health efforts has engaged a variety of commercial application providers in the field.

Representatives from any of the groups mentioned as stakeholders can function as registry sponsors or developers. A distinction is made between registry *sponsors*, as the entities who fund, plan, and often select data collection content for a registry, and *developers,* as the technology and computing professionals who build the registry.

Table 25. Role of Stakeholders in Rare Disease Registries

Stakeholder	Role in Registry	Motivations for Registry Involvement
Patients and their families / caregivers	Participants	Increase knowledge about the disease; create community; facilitate development of new treatments
Patient advocacy groups	Advocates, sponsors	Increase knowledge about the disease; increase access to care; support training and research in disease area; raise profile of the disease to encourage funding for more research
Clinicians/Investigators	Data contributors	Increase knowledge about the disease; learn from registry community; gather data to refine complex or undefined diagnoses; develop and inform treatment guidelines
Academia	Principal investigators, scientific advisors	Improve understanding of disease; create data source for research in disease area
Biopharmaceutical industry	Sponsors, developers	Understand natural history of disease to design better clinical trials and evaluate potential relevant clinical endpoints; fulfill post-marketing commitment; provide patient pool for interventional studies; determine potential market share and access patients; publications
Government / Regulatory agencies / Payers	Sponsors, recipients of information	Increase knowledge about the disease; monitor safety of approved products; evaluate cost-effectiveness and budget impact; evaluate evidence for reimbursement

Although data from registries are not a substitute for controlled trials, rare disease registry data may be the only source of information (especially about a specific product's use) available to stakeholders. This information may serve to inform industry such that a controlled trial can be determined to be feasible, designed appropriately, and well informed upon inception. Disease registry data complement trials, especially those conducted in rare diseases, for which other sources of data are rare or non-existent. Industry supports many rare disease patient registries, both disease-based and product-based, as sponsors and developers. This is particularly common in rare disorders for which the clinical development program is often abbreviated and inclusive of only a small, relatively heterogeneous subpopulation of the disease. These registries are often well received by patient groups who do not have funds to operate a

registry independently, but stakeholder objectives are not always aligned. For example, industry-sponsored registries are in some cases treatment- or product-based registries, where patients are included for study based upon treatment exposure. However, some product exposure registries create a fragmented system that does not allow researchers or policymakers to see the entire spectrum of disease.[5] These different product registries have different sponsors and collect different data (often at the behest of regulators who seek answers to different questions), rendering them difficult to combine during research. When more than one treatment exists for a given condition, the different post-marketing treatment registries are often not comparable, nor are the full spectrum data (from multiple registries hosted by multiple companies) easily accessible for academic researchers. Additionally, if patients are exposed to multiple treatments, their data might be in multiple registries, but their full experience across treatments is not appreciated.

Disease registries (rather than exposure or treatment registries) create the possibility to assess the long-term safety and benefit of different treatments, perhaps leading to treatment algorithms that allow more choices for patients and clinicians. Regulators have increasingly recognized the value of disease registries for historical comparator data and long-term evaluation (especially for drug safety) and as a complement to randomized clinical trials to "fill in the blanks" about outcomes that were not addressed in the limited controlled studies. These registries become even more important to regulators (and others involved) when the disease is rare and registries may be the only means by which data can be obtained. The marriage of stakeholder interests may create conflicts of interest for these registries that require careful scrutiny of available resources. If an effective partnership can be established and maintained, the creation of clinician and patient/caregiver communities can be a powerful agent in the success of a product in development or evaluation.

Even more effective in rare disease research is a collaborative approach in which multi-national and multi-institutional stakeholders combine resources. As resources are combined, standardization becomes more important to allow data to be compared across registries. Regulatory organizations such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) can guide standardization across multiple post-market registries within specific disease areas and promote the creation of multi-sponsor registries where appropriate. Other organizations like PARENT are facilitating cross-border collaborations to develop comparable and transferrable patient registries. Resources and tools for identifying and sharing patient registry questions, such as the PRISM library of patient registry questions[6], will support these standardization efforts.

Although the creation of a single, global registry for each disease (or group of diseases) is theoretically a sound idea, in practice it may not always be feasible or in the best interest of researchers. A viable alternative can be a network of registries and resources, such as Treat-NMD, which was launched in early 2007 and consists of a network of neuromuscular disease researchers. Treat-NMD aims to create an infrastructure to promote the development of tools (e.g., core outcome sets) that industry, clinicians, and scientists need to bring novel therapeutic approaches through preclinical development and into the clinic and to establish best-practice care for neuromuscular patients worldwide.[7] Similarly, multiple registries could be connected via a centralized biorepository or biobank to provide larger sample sizes to understand disease processes and how they correlate with patient outcomes. As with any collaborative research, the challenges lie in who manages the collaboration, who funds it, and what governance infrastructure is required to bring together researchers who may be reluctant to share their data. The availability of indices

of registries [e.g., OrphaNet[8] in Europe and the proposed Registry of Patient Registries (RoPR) in the U.S.[9]] is helpful for identification of potential data sources and collaborators.

3. Implementation of a Rare Disease Registry

3.1. Patient Population

Because patient registries can collect clinical information from larger, more heterogeneous populations than those included in a clinical trial, they are becoming increasingly valuable, particularly for diseases affecting very small patient populations, such as lysosomal storage disorders and for specific populations such as children.[10] Whereas selection of patients may be highly restrictive in general disease registries, rare disease registries often have more liberal criteria for inclusion. In many cases, a physician diagnosis, rather than the more common strict classification schema, may be sufficient for inclusion in a rare disease registry. Reasons may include: 1) no classification criteria exist; 2) knowledge of the rare disease is so limited that being more inclusive is desirable; and 3) the population is so small that being more inclusive is desirable. With some exceptions, rare disease registries typically do have broad inclusion criteria and attempt to enroll most, if not all, eligible patients within a targeted geographical area. Although they may not be sufficient for population-based estimates of disease, these data sources can be used to estimate the numbers of affected patients and the number of patients potentially available for research and can enable the mobilization of disease-specific communities and advocacy action. Since a large proportion of recognized rare diseases are genetic in origin, enrolling family members greatly improves understanding of the disease, but may create additional complexities around confidentiality, logistical issues (e.g., different last names and other tracking issues), and considerations for enrollment of minors. The issue of 'study fatigue' should also be considered when developing patient enrollment plans. Because of the limited numbers of available patients, some patients may be asked to participate in multiple studies over time. Patients may become overtaxed by frequent participation in studies and reluctant to join new studies.

For registries examining treatment-related outcomes, the challenges in creating an inclusive patient cohort include differences in health care delivery systems, local regulations, and budgetary considerations that create barriers to care and/or specific treatments. For example, if a disease is rare, a manufacturer may choose not to go through the rigorous process required to have it approved or priced locally – such as in a small country - as the number of patients who might ultimately use the product does not support the cost of time and effort. This may create difficulties in enrolling a representative patient cohort from such regions.

3.2. Data Collection

Most registries are tempted to (and often do) include as many data elements as possible in order to glean as much information as possible from their study population. This often leads to increasing respondent and investigator burden, high rates of discontinuation, and substantial challenges in data management. In some registries, these drawbacks may be offset by the ability to continue to recruit additional patients and/or the availability of sufficient numbers of patients already enrolled despite drop out. This is rarely the case, however, with rare disease registries. Thus, balancing the need for a broad data set with the burden of data collection is highly important for rare disease registries.

In many respects, data collection for rare disease registries is similar to data collection for other types of registries. Like other registries, rare disease registries aim to collect a uniform set of data on each patient. Data elements should be clearly defined to ensure consistency in interpretation across participating sites, and data collection and management procedures should be designed to support the collection of high quality data. Other chapters in this document discuss these concepts in more detail as they apply to registries generally. However, while many of the best practices described elsewhere in this document are applicable to rare disease registries, rare disease registries face unique data collection challenges that are not addressed by those best practices. In particular, rare disease registries may encounter additional hurdles when attempting to use common data elements, selecting quality of life or patient-reported outcome measures, collecting biomarkers, obtaining long-term followup data, and assuring data quality.

3.3. Creating Efficiencies in Registry Development

A major step in the development of any registry is the selection of the data elements. This can be time-consuming and resource-intensive, particularly when multiple stakeholders are involved in defining the data set. As noted in Chapter 4, the primary goals in selecting data elements are to ensure that the necessary data are collected to achieve the objectives of the study and that the data set is not overly burdensome so as to limit participation in the registry. A critical component of developing the data set is defining the data elements and determining how each piece of data will be collected. Many registries develop and define their own data elements. This approach can be costly, and it limits the ability of data from the registry to be linked or compared to data from other registries or data sources. It is more challenging to standardize the data collection for rare diseases, as the understanding of the disease is likely to be limited and, until recently, established standardization efforts were limited.

Common data elements may offer a potential solution to some of these issues. A common data element (CDE) can be defined as "a data element that can be consistently collected across all clinical studies."[11] CDEs include standard definitions, code lists, and instructions so that the data are collected and stored in the same manner by each participating site, in each study. CDEs may be general, meaning they can be used across disease or therapeutic areas (e.g., demographics, vital signs)[12] or disease-specific, meaning they are designed for research in a particular disease area (e.g., congenital muscular dystrophy).[13] By using CDEs, registries may be able to reduce the time and effort involved in developing a data set and to enable the registry data to be linked or compared to data from other studies using the same CDEs.

CDEs are particularly important for rare disease research. CDEs may lower the cost of developing a new registry, making registries more accessible for diseases where funding is limited. CDEs may also enable data from multiple small registry projects to be linked or compared to increase knowledge about the disease. The Institute of Medicine noted the potential importance of CDEs for rare disease research. In the 2010 report, *Rare Diseases and Orphan Products: Accelerating Research and Development*, the IOM stated, "The [National Institutes of Health] NIH should support a collaborative public-private partnership to develop and manage a freely available platform for creating or restructuring patient registries and biorepositories for rare diseases and for sharing de-identified data. The platform should include mechanisms to create standards for data collection, specimen storage, and informed consent by patients or research participants."[14] Recognizing the potential value of CDEs, the National Institutes of Health recently funded the PRISM (Patient Registry Item Specifications and Metadata for Rare Diseases) project. The objective of the PRISM project, which is administered through the National Library of Medicine and supported by the Office of Rare Disease Research (ORDR), is to develop a library of standardized

questions that will be relevant to a broad mix of rare diseases and that can be used to develop new registries or to update existing registries. Ultimately, the project aims to develop tools that will support the rapid implementation of new rare disease registries, the revision of existing registries, and interoperability between rare disease registries and other data sources.[15,16]

In January 2010, the NIH and ORDR hosted a workshop entitled "Advancing Rare Disease Research: the Intersection of Patient Registries, Biospecimen Repositories, and Clinical Data,"[17,18] which launched the development of the Global Rare Disease Registry and Data Repository (GRDR), a web-based data registry that will link existing registries, future registries, and biorepositories.[19] Two significant work results are expected out of this initiative. The first is a two-year pilot program in collaboration with Patient Crossroads, Children Hospital of Philadelphia, and WebMD that will develop a web-based template to allow any patient group to establish its own patient registry. The second work result is a preliminary set of recommended CDEs[20] that has been drafted and has undergone revision based on feedback received from public comment. The CDEs are generally applicable to any rare disease registry. This CDE list mixes required and optional elements in the following categories: Current contact information; Sociodemographic information; Diagnosis; Family history; Birth and reproductive history; Anthropometric information; Patient-reported outcome; Medications, devices, and health services; Clinical research participation and biospecimen donation; Communication and preferences. ORDR is working closely with the Clinical Data Interchange Standards Consortium (CDISC), which has reviewed the ORDR CDEs[21] and is in the process of a similar initiative focused on common data elements for clinical trials. Planned next steps include working with the rare disease community (including clinicians, patients, and advocacy groups) to develop CDEs for specific rare diseases.

While CDEs have significant potential for rare disease registries, they do have some limitations. First, while general CDEs may be relevant for rare disease registries, these CDEs can typically only cover a small portion of a data set necessary for studying a rare disease. The currently available disease-specific CDEs tend to focus on prevalent diseases, such as cancer, cardiovascular disease, and neurological disorders. (Refer to Chapter 4 for a table of currently available CDEs.) Some of these CDEs may be relevant for some rare disease registries, but many may not be useful. Second, CDEs may change over time to reflect changes in practice or new trends in clinical research. Registries with shorter durations (1 to 2 years) may not be affected by changes in CDEs, but rare disease registries are often designed to follow patients for long periods (e.g., several years or until death). To retain the benefits of linkage and comparison, registries that use CDEs would need to update their data collection tools to reflect the changes in CDEs.

In selecting data elements for a rare disease registry, it is useful to consider using CDEs as a first step, before developing new data elements independently. Available CDEs may be relevant for basic information, such as demographics, and for some disease-specific information, and the use of these CDEs is encouraged, when possible. When CDEs are not available, a review of the literature and searches of ClinicalTrials.gov and other similar databases may identify other registries or clinical studies in the disease area. Those studies may be willing to share information on their data sets, so that the new registry can either align with those data elements to support future linkages or comparisons or perhaps learn from issues that have come up in the other studies and apply that knowledge to the development of a new data set. As noted in Chapter 4, other considerations in selecting data elements include feasibility (Are the data elements routinely collected in clinical practice?), burden (scope of data collection versus burden on

participants), and geographic variations in terminology and practice (Do disease definitions differ? Are data collected the same way in all registry locations? Do terminologies vary by country?).

3.4. Including Quality of Life or Patient-Reported Outcome Measures

Quality of life and patient-reported outcome measures (PROs) are increasingly being used in registries to understand patient experiences and preferences. In rare disease research, quality of life data and PROs may be particularly important when well-defined, widely accepted clinical outcomes are not available. The progression and mechanisms of rare diseases are often not well understood, which inhibits the identification of meaningful clinical outcomes, the development of new therapies, and the assessment of the effectiveness of existing therapies or disease management strategies. Quality of life measures and PROs may provide useful data to show that disease management strategies or treatments are effective at improving patient (and caregiver) outcomes or quality of life.

The selection of quality of life measures or PROs for a rare disease registry can be challenging. Disease-specific measures are often not available, and generic measures that were developed with consideration to more common diseases (e.g., the SF-36) are not detailed enough to capture relevant changes in the patient's (or caregiver's) quality of life. New measures may be difficult and expensive to develop, given the small number of patients, validation requirements and the need to have measures that can be used in multiple languages. As with the selection of data elements, registries may seek to identify other existing studies in the disease area and use similar measures to allow for future comparisons. When selecting measures, burden on the participant is a major consideration. The inclusion of multiple quality of life measures and PROs can be tempting, but they may deter patient participation if the burden is excessive. Considerations for selecting measures, collecting the data, and analyzing and interpreting the data are further discussed in Chapter 5.

In addition to utilizing a PRO tool, a registry may be used to validate one or more PRO instruments across a large number of centers and in some cases countries. Non-validated tools, such as patient diaries and other electronic or paper-based data collection methods (e.g., treatment logs to track compliance, symptom checklists), may also be integrated across the registry or within a subpopulation of interest.

Health economic data may also play an important role in a rare disease registry. While the major goals of the registry may be to improve understanding of the disease or to monitor treatments, an underlying objective may be to build the case for new research in the disease area and the development of new therapies. Health economic data may be useful for more broadly demonstrating the global burden of disease (GBD). Because of the rarity of the disease, the burden may not be well understood, and GBD data may be used to gain support for funding new research in the disease area. In addition, if therapies are developed for rare diseases that were once only treated with supportive care, some aspects of disease burden may improve, while other considerations, such as long-term disease management, may be introduced.

3.5. Biomarkers

Biomarkers, which may describe risk, exposures, intermediate effects of treatment, and biologic mechanisms, are an important component of rare disease research and may serve as important surrogate endpoints for health outcomes.[22] In their report on accelerating rare disease research, the IOM identified biomarkers as an important avenue. When biomarkers have been identified for a rare disease, registries in that disease area should consider collecting biomarker data as part of the registry. Registries in disease

areas where biomarkers have not been identified may also consider collecting biological specimens, physiological tests or radiographic studies, in hopes of furthering efforts to develop and validate biomarkers.[23]

When determining whether to collect biomarkers or other biological specimens, registries must consider several factors, including:

- Does the biosample need to be collected once or on an ongoing basis? If ongoing, how often?
- Does the biosample need to be examined by a central laboratory? Will multiple laboratories be needed because of geographic constraints (e.g., EU samples cannot be sent to a laboratory in the United States) or time constraints (e.g., sample processing is required within 24 hours)?
- What privacy and ethical issues will the collection and storage of biosamples introduce?
- How will the informed consent discuss the collection and storage of biosamples? How broad can the language be? Can it address as-yet unanticipated use of these samples?
- How long will the biosample data be stored? For what research purposes may it be used?

As more is learned about a rare disease and its origins, the ability to perform exploratory analyses on existing samples is critical and should be considered when a biorepository is established.

3.6. Collection of Followup Data

Collection of long-term followup data is often an important component of debilitating but not fatal rare disease registries. Many rare diseases are chronic and lifelong, meaning that registries may wish to track patients for several years or even until the patient's death. The collection of long-term followup data for rare diseases raises some unique challenges, including what type of providers should participate (specialist vs. general clinician), how to encourage retention and minimizing lost to followup patients.

Many patients with rare diseases see a specialist in the disease area on a regular but infrequent basis (e.g., annually) and see other clinicians on a more regular basis. The specialist may see several patients with the same disease and may have specialized knowledge of the disease; in that sense, the specialist may be an ideal candidate for registry participation. However, participation by the specialist may result in infrequent data collection on the individual patients or missing data that is collected by other clinicians. The registry may miss events that occur between specialist visits and may not obtain an accurate picture of the day-to-day impact of the disease. Participation by the clinician (or clinicians) that treats the patient on a regular basis is another option. These clinicians may only see one or two patients with the disease and they may not have specialized knowledge of the condition; however, they may be able to provide more frequent updates on the patient's condition. Both of these approaches have strengths and limitations. The most comprehensive approach is to collect data from both the clinician and the specialist. This allows the registry to gather both the specialist's overall perspective on the patient's condition and the more granular details of the patient's care. However, this approach raises privacy issues, as the registry may need to share the data collected from the specialist with the clinician and vice versa. It may also present recruitment issues, as both providers must participate in order to avoid significant missing data. The registry will also need to plan for both physicians to participate in order to avoid having duplicate patients entered into the registry.

Because the collection of long-term data is often critical to the registry's objectives, the registry must devote sufficient effort to patient and physician retention. Over time, patients and physicians may lose interest in the registry and stop participating. Patients who enrolled in the registry as a minor may change physicians and locations upon reaching adulthood and on multiple occasions. Patients may move and begin seeing a new physician, or physicians may retire and stop participating. Direct input and access to registry data by affected individuals is technically possible and would allow for ongoing registry involvement and foster retention of patients. It has been observed that patient/family entered data is reliable information but may not be as in-depth or in medical language as provided by physician. Depending on the objectives of the registry, one approach would be to facilitate patient/family entry of data to the patient registry with better design of data entry forms/screens, appropriate contact and followup with participants, and sharing of study results and summary data from the patient registry with participants.

Chapter 10.3 describes many factors that can encourage retention, as well as some potential pitfalls that may hurt retention. Rare disease registries with long-term followup components should have plans in place to monitor retention rates and should have consistent procedures for when to consider patients lost to followup. Registries that collect sufficient identifiers may also consider linking to other data sources, such as the National Death Index in the United States, to determine if patients have died. Procedures used to locate missing registry participants should be articulated in policies and procedures and communicated to participants. In addition, processes to retain patients as their status changes (e.g., from treating clinician to clinician, from being a minor to an adult) should be clearly stated and multiple contacts available for both the individual and their next of kin/designated secondary contact.

3.7. Data Analysis

Patient registries are critical for accruing a sufficient sample size for epidemiological and/or clinical research for rare diseases. In most cases, the registries are not statistically powered for hypothesis testing, and the analytic goals should focus on the descriptive techniques relevant to observational research. The uptake of common data elements could facilitate the formation of analysis datasets from the combination of multiple data in situations where two or more disease registries exist, thus increasing sample sizes.

Data collected in rare disease registries prior to the introduction of therapies that drastically alter standard of care and/or treatment guidelines can provide useful information regarding the natural history of disease. If these data do not exist, removing the effects of widespread treatment(s) from registry analysis on disease progression, particularly in highly heterogeneous disease, is challenging. An additional challenge in rare disease registries is the fragmentation of the data. Patients may contribute data sporadically, but not be completely lost to followup. If data are combined across registries (or other databases), care should be taken to identify potential duplicate patients prior to analysis, as this is more likely to occur in a limited population. Many of the other considerations for analysis (e.g., controlling for confounding, handling of missing data, loss to followup) are not unique to rare disease registry data and are addressed in other chapters, such as Chapter 2, 3, and 13.

3.8. Data Access and Communication

Because populations with rare diseases are often considered vulnerable and under-resourced, and because populations are smaller, it is important to plan for registry data access and communications. Data ownership, data access, and communication are important issues for all registries, but rare disease

registries often must pay special attention to these issues because of the broad range of stakeholders involved and the potential interest to others in the disease. Ownership of the data should be clearly specified during the planning phase of the registry and communicated to stakeholders and participants in the registry. In many cases, the data owner is the sponsor of the registry. Some registries, though, may have multiple sponsors, or the sponsor may designate that another group will own the data. In addition to ownership of the actual data, ownership of the intellectual property resulting from the registry (e.g., case report forms, patient reported outcomes tools, reports, analyses, and associated biosamples) should be clearly specified.

Rare disease registries should also develop and adhere to a data access plan. Many data access scenarios are possible. For example, the registry data may only be accessible to the data owner or the sponsor. Alternately, the registry may develop data sharing policies that allow other researchers to access the data. The registry may limit data sharing to investigators participating in the registry, or the registry may allow outside investigators to access the data. For example, an outside researcher may use data from the registry to assess incidence of a particular complication for the purposes of informing protocol development for a new study. As discussed in Chapter 2, data sharing policies should address who can access the data, for what purposes, and under what circumstances (timeframes, access fees, etc.). For example, will manufacturers be able to access data to inform the design of new clinical trials? Will researchers be able to link the data to other data sources for new studies? These types of questions should be carefully considered and addressed in data sharing policies so that all participants (including patients) are aware of the policies and plans for the registry data. Written registry policies and procedures are encouraged and required by many regulatory entities (e.g., institutional review boards).

Publication rights and plans for disseminating information from the registry should also be considered during the planning phase. This is particularly important for rare disease registries with multiple stakeholders, who may have diverse and conflicting interests, as well as considerations about academic and other interested parties not included in the registry who may wish to use these data at some later point in time. For example, a registry with strong patient advocacy group support and industry funding may need to balance the desire to publish early (to share information with the patient community) with the desire to publish later (to protect proprietary information related to treatment development). Clear publication plans that are shared with registry stakeholders can help to avoid disagreements once the registry has begun collecting data, and can promote registry transparency.

Like all registries, transparency is important for rare disease registries, and perhaps more important.[24] Because rare diseases have a limited pool of patients, they need to maintain a highly motivated patient community engaged and actively participating in the registry. Transparency in registry operations, analyses, and publications can help to reassure participants that the registry is fulfilling its objectives and continues to be a worthwhile endeavor. This may take the form of regular updates on registry enrollment and data collection, newsletter updates from principal investigators, and sharing information about abstracts or publications based on registry data. Transparency also requires full disclosure to participants about the use of their data, the registry funding sources, and any underlying goals or motivations for the registry.

3.9. Governance

The governance of a rare disease registry can be extraordinarily simple or, more often, fairly complicated. Complexity stems from the variety of stakeholders involved and their different agendas, as well as the geographical and cultural distances between the interested parties, particularly for international registries. Simplicity depends upon having clear goals and adept leadership. Registry leadership may be in the form of an Advisory Board or other leadership committee. Advisory boards and general governance principles are discussed in Chapter 2.6.

Rare disease registries present unique governance challenges because they often represent collaborations with many stakeholders and may be international in scope. Some examples are included below.

- **Funding.** If not centrally funded, who takes responsibility for raising money, writing grants, and securing the necessary funds for the operation of the registry? If fully funded, what role in decisionmaking does the financial sponsor(s) have? What are the start-up costs versus maintenance costs?
- **Privacy.** Patients with rare diseases are more vulnerable than most to being identified by their health information. How does the registry protect the privacy of the individuals and families while at the same time creating a database of information and resources for the benefit of all persons having the rare disease of interest?
- **Outreach.** How does the registry identify affected and interested persons for participation in the registry?
- **Information.** What database is needed for the registry? What demographic, clinical, and/or longitudinal databases are needed? How will the registry adapt as new data needs are identified?
- **Ownership.** Who owns the information collected by the registry? For a tissue repository, who owns the materials in it?
- **Agenda.** Who sets priorities and establishes the work plan for the registry? What are the respective roles of the stakeholders in setting the agenda?
- **Collaborations.** Does the registry governing body create collaborations or can individual participants make collaborative agreements? What approvals are required? How are conflicts avoided and handled?
- **Publications.** Who takes responsibility for determining the publication plan, submitting abstracts, writing journal articles, and otherwise publishing about the activities of the registry? Who does the work? Who gets the credit? Are all of the professional and nonprofessional participants treated equally?

4. The Future of Rare Disease Registries

Existing literature suggests that rare diseases occur infrequently and there is a scarcity of information; however, in reality, difficulty in correct diagnosis and appropriate identification of patients with rare diseases is a global issue that precludes knowledge of these patients. The lack of information reflects the uncertainties in diagnostic criteria and perhaps even inadequacies in data gathering procedures. As the patient community continues to grow throughout the world, fostered by electronic communication and social media, knowledge of the prevalence of rare diseases will increase and access to patients will be more readily available. Improved access to information on rare diseases continues to expand as rare

diseases are addressed on a global basis and more people are aware of the informational needs of the rare diseases community.

The increasing interest in rare disease patient registries by a range of stakeholders will likely lead to the development of many more patient registries. In the absence of a central health care system with all demographic and clinical data in one place, individual registries for different diseases are likely, each with a smaller and smaller set of patients. Organizational collaboration and shared resources, plus engagement of the rare disease community, are needed to move research and knowledge forward. These registries may be used to identify new pathways for treatment, develop clinical research tools such as endpoints, scales, or outcome measures, and recruit potential participants for clinical trials. However, the development of each individual registry requires significant effort and resources. For some diseases, well-organized private foundations or manufacturers with an interest in product development or monitoring are capable of developing effective registries. For many other diseases, there are few resources to support an independent registry. Some efforts are underway to develop linked networks of registries for rare diseases. For example, the NIH has put forth the idea of creating a federation of Internet-based registries for rare diseases. The goal of this effort is to reduce the costs of developing and running a registry. The idea was part of the discussion at a January 2010 conference on patient registries and rare diseases sponsored by the NIH's ORDR.[25]

The proliferation of registries and the need for global multi-disciplinary cooperation for rare disease research creates an urgent need for standards and best practices for these types of patient registry projects. The large number of registries and the various purposes and stakeholders for each complicate any attempts to inventory, standardize, or prescribe good design features for patient registries in general. As previously described, ORDR, in collaboration with the rare diseases community, is working to establish the Global Rare Diseases (Patient) Registry and Data Repository (GRDR) to enable analyses of data across many rare diseases. ORDR has developed and posted for public use a set of general CDEs to be used for rare diseases; these have gained support at the NIH, CDISC, and in the international community. At a recent meeting of the International Rare Diseases Research Consortium (IRDiRC) in Bethesda, the CDEs were accepted as a starting point for rare diseases. The ORDR also will make available to all patients/patient advocacy groups a web-based template to establish a patient registry with the ability to link patients' data and medical information to their biospecimens. In addition, ORDR will encourage all individuals and organizations that elect to develop a patient registry to participate in the Registry of Patient Registries to increase public exposure to these vital research tools. The next stage is to develop organ/system specific and disease-specific CDEs developed as collaborative efforts of patients, research investigators, industry clinicians, and other partners in the rare diseases community. ORDR continues to collaborate with NIH research institutes to identify existing rare disease patient registries and utilize the common data elements.

Because of the increase in registries, more efficient ways to implement and maintain rare disease registries and maximize utility for all stakeholders will be required. Technological advances, such as means for integrating data sources, should result in processes that are more streamlined for the data provider as well as the analyst. The growth of web-based patient communities and social media may also be increasingly integrated into registry data collection and conduct, as community building across geographical boundaries continues to become simpler.

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Case Examples for Chapter 20

Case Example 43. Using a Registry To Assess Long-Term Product Safety

Description	The International Collaborative Gaucher Group (ICGG) Gaucher Registry aims to enhance the understanding of the variability, progression, and natural history of Gaucher disease, with the ultimate goals of better guiding and assessing therapeutic intervention and providing recommendations on patient care to the medical community that will improve the outcomes for patients affected by this disease around the world.
Sponsor	Genzyme, a Sanofi company, Cambridge, MA
Year Started	1991
Year Ended	Ongoing
No. of Sites	700+ sites have enrolled patients
No. of Patients	More than 6,500 with open-ended follow-up

Challenge

Rare diseases pose special and unique research challenges. The small number of affected patients often results in limited clinical experience within individual health care centers. Therefore, the clinical description of rare diseases may be incomplete or skewed. The medical literature often consists of individual case reports or small case series, limiting understanding of the natural history of rare diseases. Furthermore, randomized controlled trials with adequate sample size and length of followup to assess treatment outcomes may be extremely difficult or not feasible. The challenge is even greater for rare diseases that are chronic in nature, where long-term followup is especially important. As a result, rare diseases are often incompletely characterized and lack published data on symptomatology, disease manifestations, and long-term treatment outcomes.

Gaucher disease, a rare enzyme deficiency that affects fewer than 10,000 known patients worldwide, illustrates many of the challenges facing researchers involved in rare diseases. Gaucher disease has three clinical presentations: Type 1, nonneuronopathic; Type 2, acute neuronopathic; and Type 3, subacute neuronopathic. Physicians who encounter patients with Gaucher disease typically have just one or two affected patients in their practices; only a few physicians around the world have more than 10 to 20 patients with Gaucher disease in their care. Understanding Gaucher disease is further complicated by the fact that it is a highly heterogeneous and rare disorder with variable progression among patients; a patient cohort from a single center may represent a subset of the entire spectrum of disease phenotypes.

The rarity and chronic nature of Gaucher disease also pose challenges in conducting clinical research. The clinical trial that led to U.S. Food and Drug Administration approval of enzyme replacement therapy (ERT) for Gaucher disease (Ceredase®, alglucerase injection) in 1991 was a single-arm, open-label study involving only 12 patients followed for 9–12 months. In 1994, a recombinant form of ERT was approved

(Cerezyme®, imiglucerase for injection) based on a randomized two-arm clinical trial comparing Ceredase and Cerezyme in 30 patients (15 in each arm) followed for 9 months.

Proposed Solution

Established in 1991, the registry is an ongoing, international, longitudinal disease registry, open to voluntary participation by physicians who care for patients with all subtypes of Gaucher disease, regardless of their treatment status or treatment type. Data on patient demographics; clinical characteristics; treatment regimen; and laboratory, radiologic, and quality-of-life outcome measures are entered and analyzed to address the research challenges of this rare disease. Because of the rarity of Gaucher disease, it is important to create and maintain a reliable, comprehensive registry that serves as an educational resource not only for physicians but also for patients and their families and caregivers. Responsibility for the use, integrity, and objectivity of the data and analyses is invested in the ICGG Board of Advisors, which consists of physician-investigators worldwide who are not employees of the sponsor and who advise on the medical and scientific agendas of the registry.

Results

The registry has longitudinal data on more than 6,500 patients from more than 700 health care centers in more than 60 countries. The follow-up period is open-ended, and the registry currently has up to 20 years of follow-up data from individual patients. The registry has collected more than 50,000 patient-years of followup during the past 21 years. Physician participation and patient enrollment have increased consistently from year to year since 1991.

Analyses of the extensive body of longitudinal data have increased knowledge of the disease in a broad range of topics, including the natural history of Gaucher disease; phenotypic and genotypic variation among patients; diagnosis, treatment, and management of Gaucher disease; disease manifestations in children; long-term treatment outcomes for ERT; bone disease and complications associated with Gaucher disease; and neuronopathic Gaucher disease. Data generated from the registry have been published in nearly 30 key articles and have provided much needed and important insight into this rare genetic disease.

In 2002, the registry published the clinical outcomes of 1,028 patients treated with ERT with up to 5 years of follow-up. As more data have been gathered through the registry over the past decade, long-term outcomes in patients with Type 1 Gaucher disease after 10 years of ERT have become available, thus providing new reference benchmarks for assessing clinical responses to ERT for various disease parameters. Other more recent publications based on analyses of data from the registry focused on important specific aspects of Gaucher disease, such as the effects of early intervention with ERT on the incidence of bone pathology, demographic and clinical characteristics of patients with neuronopathic Gaucher disease, ERT dose-response relationships for disease parameters in patients with Gaucher disease type 1, and phenotypic heterogenicity and genetic variation among patients.

Along with the growth of the registry and available data on Gaucher disease, interest in special patient populations and specific aspects of Gaucher disease continually emerge. As a result, research initiatives into disease sub-populations have been launched recently: Neurological Outcomes research, which will begin to evaluate the neurologic manifestations of Gaucher disease and the effects of treatment on

these complications; and the Pregnancy Subregistry, which will track the management of Gaucher disease during pregnancy, as well as pregnancy outcomes.

The collective clinical experience of the registry led to the development of recommendations for evaluation and monitoring of patients with Gaucher disease. The analysis of registry data on treatment outcomes has facilitated the establishment of therapeutic goals for patients with Type 1 Gaucher disease. Together, these publications have formed the foundation for a consensus- and evidence-based disease management approach, something usually only possible for much more common diseases. In 2008, a benchmark analysis was published that documented the achievement of therapeutic goals after 4 years of ERT among registry patients.

As disease awareness increased over time, health care providers have sought more direct access to general disease and patient-specific disease information. Therefore, when registry changed its technology platform in 2011, it established two key objectives: to simplify data entry to help keep data complete and accurate, and to support the community's increased interest in access to data, aggregate reports, and collaborative expertise. To help meet these goals, the registry ensured that the new platform included functionality that allows physicians direct access to aggregate and patient-specific reporting as well as the ability to download their own data to support their own research. This important application of technology enables the registry to "give back" supportive and research tools to those who contribute to the overall registry dataset. This includes the availability of data to address clinical and scientific questions; useful disease management tools, such as interactive patient case reports that a physician can share with other healthcare providers and with patients themselves; and a larger, better-connected, worldwide community of physicians and allied health providers who can share information, identify trends, improve best practices, and build awareness of Gaucher disease that will optimize patient outcomes.

Key Point

For rare or ultra-rare conditions, an international, longitudinal disease registry may be the best or only feasible way to comprehensively increase knowledge about the clinical characteristics and natural history of the disease and assess the long-term outcomes of treatment.

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Case Example 44. Studying Rare Diseases in an Existing Registry Population

Description	The National Cooperative Growth Study (NCGS) collected data on children with growth disorders who were treated with a specific growth hormone (GH). The purpose of the multicenter, observational, post-marketing surveillance registry was to collect long-term safety and effectiveness information on the GH preparations, with the goals of better understanding the growth response to GH therapy and establishing a safety profile in large populations of different patient diagnostic groups.
Sponsor	Genentech, Inc.
Year Started	1985
Year Ended	2010
No. of Sites	More than 550
No. of Patients	65,205

Challenge

The registry was launched following FDA approval of recombinant human growth hormone (rhGH) in 1985. While the primary purpose of the registry was to monitor the safety and effectiveness of rhGH in all pediatric patients undergoing this treatment, there was a lack of sufficient numbers of patients in the clinical trials in each subgroup of patients for whom the drug was indicated to establish a true picture of their medical risks and what interaction or impact GH had on their medical safety. There was particular interest in studying girls with Turner syndrome (TS), a rare chromosomal abnormality which is known to be commonly associated with multiple medical conditions.

Proposed Solution

Pediatric patients with growth disorders were voluntarily enrolled in the registry when therapy with rhGH was initiated, and followed until discontinuation. The median length of followup for patients in the registry is 3.3 years, allowing for longitudinal analyses of the natural history of growth disorders and their treatment, and addressing physician queries on the long-term safety and effectiveness of rhGH therapy for their patients. The broad enrollment criteria of the registry enabled capturing a meaningful sample of patients with rare syndromes or diseases. For example, the registry population included over 5000 patients with TS.

Results

For 25 years, the registry monitored the safety and efficacy of rhGH therapy in 65,205 children with growth disorders treated in more than 550 sites in the US and Canada, with more than 800 investigators, and accrued over 220,000 patient years of observation. During this time, analyses resulted in more than 100 publications on safety, dosing, height prediction outcomes, subgroups of patients, and regulatory safety assessments with over 1,200 citations in the research literature. The registry remains the largest North American repository for auxological and clinical outcome data for rhGH-treated children with growth-related disorders.

Analyses were conducted on 5220 registry patients with TS, resulting in a seminal paper being published which described the safety profile of GH in this condition and highlighted the natural history of many of the known medical conditions these patients have. The safety profile included assessment of cardiac risks, development of autoimmune disorders, and detected occurrence of a disproportionate number of cases of pancreatitis compared to the other patient groups in the NCGS. This later finding contributed to a recent label change warning of the risk of pancreatitis for all growth hormone products, including a reference to the published data that suggests higher risk in patients with TS. In addition, a sub-study in the registry assessed the degree to which pediatric endocrinologists were following recent guidelines for screening of concurrent medical conditions in TS. The guideline sub-study revealed that, in a cohort of 955 girls, screening for cardiac, renal, and hearing abnormalities was not occurring at the expected rate. The clinical implications of these studies were a broader picture of the natural health history of girls with TS as well as specific issues of safety with respect to growth hormone.

The registry closed enrollment in 2010, but the database continues to be a resource for practicing physicians facing patient treatment decisions, averaging 1-2 queries per week from former investigators on the safety and effectiveness of GH treatment. Recent examples of query topics include patients with TS, safety in patients with intractable seizures, medulloblastoma and secondary malignancies associated with GH, primary pulmonary hypertension, and other conditions. One query, on rhGH use in GH deficient or idiopathic short stature patients treated with stimulants for ADHD, led to a publication that found no significant differences in safety or effectiveness of rhGH treatment for these patients in comparison to non-ADHD treated patients.

Key Point

A large registry can provide a resource of study subjects for focused investigations on specific rare diseases. Even after study closure, registry data can be a useful resource for continued investigations, and for informing treatment in clinical practice.

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Case Example 45. Site Motivation and Retention in Rare Disease Registries

Description	The Digital Ulcers Outcome (DUO) Registry collects data on patients with systemic sclerosis in an effort to describe digital ulcers disease history, clinical and patient-reported functional assessment status and treatment pattern at the time of enrollment, disease course, and patient management during followup. For patients treated with bosentan, data is collected on physician adherence to labeling guidelines and safety events.
Sponsor	Actelion Pharmaceuticals
Year Started	2008
Year Ended	Ongoing
No. of Sites	Over 350
No. of Patients	3,609

Challenge

Systemic sclerosis (Scleroderma) is a rare disease affecting less than 2/10,000 persons worldwide. Digital ulcers affect nearly 30% of patients with this disease, resulting in substantial morbidity such as gangrene and amputation. Despite the severity of digital ulcers, very little is known about this complication due to the rarity of the underlying condition. To improve understanding of this condition, data are needed from specialized participating Scleroderma centers (sites).

The DUO Registry was mandated by the European Medicines Agency (EMA) as a post-approval licensing requirement for the expanded indication of bosentan to treat digital ulcers. The registry, which operates in 18 European countries, is observational and voluntary in nature, and participating sites are reimbursed solely for data entry time. After four years of operation, motivation of the participating physicians started to stagnate, and the sponsor observed a decrease in followup data entry. Because the registry was mandated by the EMA and because of the paucity of outcomes data available about digital ulcers, the sponsor sought to increase participation and, in particular, increase the collection of followup data.

Proposed Solution

The sponsor identified academic and professional interest in the registry's findings around digital ulcer management as one of the primary motivators for investigators to participate in the study. To respond to this interest, the sponsor implemented new efforts to engage investigators and regularly inform them of the study's progress. Efforts included the use of newsletters to provide enrollment updates and tips on using the electronic data capture system, presenting abstracts in scientific congresses, and distribution of letters from the registry steering committee to the investigators encouraging them to enter followup data. An in-person investigator meeting was held, where the registry's scientific committee discussed registry findings with the investigators. The sponsor also established a process for investigators to suggest publication ideas and determined that all publications of registry data would include the phrase, "and DUO Registry investigators," in the author byline.

Results

From 2011 to 2012, the number of patients having at least one follow-up visit increased from 63% to 73%, and mean number of visits per patient increased from 1.7 to 2.6. The registry has now enrolled over 3600 patients.

The steering committee and registry investigators published the first original article on registry data in January 2012, reporting on data from 2439 patients and confirming the disease burden of digital ulcers in systemic sclerosis patients. The sponsor had received feedback that the shared authorship is valuable to some investigators and a major motivating factor for participating in the registry.

A poster highlighting the current variation in treatment of digital ulcers across Europe and stressing the need for a concentrated approach to establish disease management practices was presented at the European League Against Rheumatism 2012 Annual Congress.

Key Point

Site engagement is particularly important in rare disease registries, because of the limited number of patients. Consistent communication highlighting study objectives and achievements, visibility at scientific meetings, and sharing authorship or acknowledgement on publications can bolster investigators' motivation.

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Chapter 21. Pregnancy Registries

1. Introduction

A pregnancy exposure registry is an observational prospective cohort of women receiving a biopharmaceutical product(s) of interest as part of their routine clinical care who are enrolled voluntarily during gestation, before outcomes can be known. Participants are followed until the end of pregnancy or longer to systematically collect information on specific pregnancy outcomes and evaluate their frequency relative to a scientifically valid reference population(s).[1-3] Specific examples of pregnancy registries can be found on the Food and Drugs Administration (FDA) website.[4]

This chapter reviews the "why, how, and who" of conducting pregnancy registries. The chapter first discusses why pregnancy registries are needed to assess risks and benefits of medications during pregnancy. Second, the chapter describes the distinctive methodological aspects of these registries, including design, study population, enrollment and followup of pregnant women, ascertainment and definition of exposures and outcomes, reference groups, statistical power, and validity issues. Third, the chapter takes a more pragmatic approach and presents key operational aspects such as protocol structure, recruitment and retention of participants, methods of data collection, when to release findings, role of advisory boards, and challenges of global designs. Finally, characteristics to consider when evaluating pregnancy registries are described. Case Examples 46, 47, 48, and 49 offer some descriptions of pregnancy registries.

2. Justification

All patients in need of treatment should have access to medications that have been adequately studied and be provided with information to assess the risks versus the benefits of using the medication. Collecting postmarketing data on the safety of medications during pregnancy is commonly done through the use of pregnancy exposure registries or pregnancy disease registries that collect treatment information. Pregnancy registries are prospective observational studies specifically designed to collect clinically relevant data and provide information for treating or counseling not only women who are pregnant but also women of childbearing potential. In 2002, the FDA published its guidance for pregnancy registries[2] with a goal of encouraging the regular use of more formal, prospective study designs to obtain clinically relevant human data that can be used in product labeling. Similar guidelines were published by the EMA in 2005.[5] In 2007, the Food and Drug Amendments Act (FDAAA) provided the authority under Title IX[6] to require pregnancy registries as a post marketing requirement (PMR). Pregnancy registries are now required at the time of a new drug approval when there is a safety concern or when there is a need to gather data on the use of the product in pregnancy based on the following circumstances: 1) prior knowledge of the product suggests a safety concern based on the pharmacologic or chemical class, or on data from animal studies or clinical trials; 2) the product will be indicated for use during pregnancy (e.g., vaccines and medications for chronic illness); or 3) there is a high likelihood of use in females of reproductive age such that inadvertent exposure during pregnancy may be expected.

For non-pregnant individuals, safety and efficacy data that yield such information are derived from well-controlled clinical trials conducted prior to a drug's approval. When it comes to pregnant women, however, the situation is different. Clinical trials rarely include pregnant women because there is a lack of safety information on the drug's use in pregnancy.[7, 8] As a consequence, most information regarding

the safety/risk profile of drugs during pregnancy is collected after the drug has been approved and used by pregnant women intentionally or unintentionally – intentionally because some conditions require treatment during pregnancy, and unintentionally because approximately half of all pregnancies in the United States are unplanned,[9] so embryo/fetal exposure to medications can occur before pregnancy is detected.

Tests in animal models are a regulatory requirement for new drugs and biologics prior to approval. In some cases, these animal toxicology studies can provide a means to detect teratogenic effects. Often however, results are not easily translated into human risk because of variations in teratogenic response among species.[10] In addition, animal toxicology studies are designed so that at least one dose tested will provoke an adverse toxic response. The results at those dose levels may not predict those that might be observed at the intended therapeutic doses used in humans.[11]

In humans, passive data collection such as the FDA Adverse Event Reporting System (AERS) can suggest potential drug safety issues for further study. The system includes any patient population that may have been exposed to the drug. Reporting to the database is voluntary (although required for manufacturers) and underreporting is a significant issue with extent of reporting thought to vary substantially depending on the drug, the indication for use, and the nature of the adverse event.[12, 13] There is no reference group and no information on the number of individuals taking the drug who did not have an adverse event. It is often not clear whether the adverse event reported to AERS is a medication-related event, an event resulting from the underlying illness, or a coincidence. Since adverse pregnancy outcomes such as pregnancy losses and congenital malformations are relatively common, they will inevitably occur among exposed individuals; selected reporting of exposed cases can lead to false alarms. Consequently, although data from AERS can be useful for identifying initial signals of adverse events, it cannot be used to quantify risks for a particular product or to compare risks between drugs.[14] Similarly, case series published in scientific journals cannot distinguish chance from causation or be used to quantify and assign teratogenic risks.

Information on human teratogens must come from adequately controlled epidemiologic studies, which include case-control and cohort designs. Case control studies identify births with the outcome of interest (e.g., a specific birth defect) and compare their frequency of exposures to that in a control group without this outcome. This design offers advantages in detection and confirmation of associations between prenatal exposure to the medication and the risk for rare events.[15] However, case control studies have some limitations. They collect information on exposure retrospectively, rarely have enough sample size to evaluate infrequently used medications, and can estimate relative risks but not the absolute risks associated with the drug.

Follow-up studies of pregnant women have the advantage of identifying drug exposure before the adverse outcomes are recognized. In non-pregnant populations, health care utilization databases such as Medicaid claims files or records in large health maintenance organizations have become a standard source of information for drug safety studies.[16] These databases are a resource for large-scale observational post-marketing studies because they offer the ability to study rare consequences of drug use. Some of these databases have limitations for the study of pregnancy outcomes because they do not routinely record evidence of pregnancy (e.g., estimated date of conception) or provide child-mother linkages. Important reproductive information, such as gestational age at birth, birth weight, and maternal reproductive history,

is rarely available.[17] Moreover, when exposure to the specific drug of interest involves a small fraction of the pregnant population, even these large cohorts are constrained in their statistical power. In this scenario, concentrating on women exposed to selected drugs through a pregnancy registry can increase efficiency. However, the FDA-funded Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) has established collaboration among a selected group of large administrative databases with the ability to link mothers and babies and with linkage to birth certificates, which contain additional information.[18] This resource will represent an important tool to study outpatient dispensing of medications during pregnancy and a number of validated pregnancy outcomes.

3. Pregnancy Registry Objectives

The overall purpose of pregnancy exposure registries is to provide human data on the safety of biopharmaceutical products during pregnancy.[1, 19] Pregnancy registries should have specific primary and secondary objectives defined *a priori* in a scientifically sound study protocol.[2] Many exposure registries have as their primary objective to "assess the risk of major congenital malformations" in the offspring of women exposed to a given drug just before or during pregnancy. Implicit in this objective is to determine whether that risk is higher or lower than expected. Registries can evaluate multiple maternal, obstetrical, fetal, and infant outcomes, from pregnancy complications to developmental delays. Moreover, they may provide an opportunity to evaluate not only the safety, but also the effectiveness of drugs, as well as the risks associated with untreated diseases during pregnancy. They can also evaluate the effect of dose, gestational timing of exposure, and effect modification by maternal characteristics.[1]

Since the ultimate goal is to inform the decisions of medical care providers and patients, it is in the common interest of all the parties to initiate the registry as soon as possible after marketing authorization, use proactive enrollment strategies (i.e., if possible, broaden the source population to obtain, for example, 1,000 exposed women in one year rather than 100 per year for 10 years), and analyze the data and report findings on a regular basis.[2] As more data accumulate over time, the registry can provide narrower boundaries of uncertainty around the point estimates, which leads to increasing assurance of relative safety or more precise quantification of relative risks. These issues are discussed more extensively in Sections 17 and 17.9 below, respectively.

4. Design

Whether stated or not, one scientific question in the evaluation of drugs during pregnancy is often "*what would have been the outcome of this pregnancy had the woman not been exposed?*" Since the counterfactual outcome for a given pregnancy is unknown, the closest strategy to respond to this question would be to randomize a group of women periconceptionally to either the drug of interest or a reference group and follow them in a blinded manner until the outcome of interest is fully assessed. This design would ensure that the groups only differ in their drug exposure and that the same methodology and clinical judgment are used to assess the outcomes. The reference group could be randomized to placebo, if not-treating were clinically acceptable, or to an alternative therapy, and the comparative efficacy and safety of two or more therapeutic options could be evaluated. However, since for ethical reasons pregnant women are rarely included in sufficient numbers in randomized controlled trials (RCT) during the process of drug development, the safety and effectiveness of drugs during pregnancy needs to be studied in post-marketing non-randomized studies.[3, 19]

The specific design of a pregnancy registry is determined by its purpose.[1] To rule out strong teratogenic effects (e.g., over 20% risk of malformations after prenatal exposure to thalidomide), enrollment of 100 exposed pregnancies in a simple uncontrolled cohort might suffice. The effect of major teratogens is so large as to overwhelm the potential impact of common methodological biases on relative risks. However, most known teratogens are associated with a more moderate increase in the risk of relatively rare malformations. [20] To detect moderate teratogens, registries need to enroll a larger number of gestations and be carefully designed.[19]

Although the same rigor and most principles of RCTs can be applied to any observational study, the lack of randomization calls for additional epidemiological methods.[21] This chapter discusses in the next sections how pregnancy registries differ from RCTs; how deviation from RCTs standards can compromise the validity of results; and how biases can be minimized through collection of detailed data on exposure and other maternal characteristics, close followup, accurate assessment of outcomes, and inclusion of comparable reference groups.

5. Study Population: Who and When

Through clear inclusion and exclusion criteria, registries target a well-defined study population that, ideally, should be closer to real clinical practice than the selected populations of a RCT. However, to the extent that pregnancy registries rely on patients or their health care providers to hear about the registry, to contact the registry, and to agree to participate, there is the potential for selective enrollment. Women who do participate might differ systematically on factors related to the pregnancy outcome from the population of exposed pregnant women who are not part of the registry. Therefore, baseline risks in the registry population might differ from those in the general population of women using the drug of interest.

In assessing the relative risks associated with the drug, there is often a tradeoff between generalizability and validity. A population-based sampling strategy can be logistically complicated and would arguably estimate a similar relative risk since a teratogenic effect found in participants would probably apply to "non-volunteers" as well. On the other hand, inclusion of non-motivated individuals might increase losses to followup, misclassification of information, and the variability and impact of confounders.

A peculiarity of pregnancy registries is that the population can be defined based on women, pregnancies, or fetuses. A woman might have more than one pregnancy, and she might enroll in the same registry more than once. Clustered analyses are often used in this situation. In addition, multifetal gestations result in more than one fetus "enrolled" within the same pregnancy. Although there may be several ways of dealing with multiple gestations, it is prudent to collect information from all the fetuses. When reporting risks, whether using fetuses or pregnancies as the unit of analysis, both the numerator and denominator should be consistent with the choice.[22]

6. Enrollment and Follow-up

An ideal pregnancy cohort would include women at conception and follow them for months beyond delivery. However, that rarely happens for logistical reasons, and, consequently, pregnancy cohorts have some degree of unintended truncation on both sides of the ideal followup. Left truncation occurs because followup can only start after women realize they are pregnant (in patient-initiated enrollment in registries) or health care providers identify the pregnancy in a patient (in clinician-initiated enrollment in registries), and the process of enrollment itself can further delay the inclusion. Right truncation occurs because

followup would end with unknown outcomes when there are losses to followup or pregnancy terminations without fetal autopsy.

As a result, time from enrollment to end of followup can range from 1 month to over 1 year. In any study, longer followup periods naturally lead to higher opportunities for diagnosis and therefore larger cumulative risk estimates and statistical power. As discussed later, inclusion of either prenatal diagnoses or outcomes identified during infancy would result in higher risks than restriction to delivery hospital discharge diagnoses. More worrisome in pregnancy registries is that selection bias can be introduced if the outcome explicitly or implicitly affects enrollment (e.g., a known outcome affects eligibility or influences self-selection) or retention (e.g., exclusion of study subjects after an abortion or neonatal death) into the cohort.

6.1. Enrollment

Registries should include women as soon as possible after conception, or even earlier at pregnancy planning stages, to allow the evaluation of early pregnancy events. For instance, pregnancies enrolled earlier in gestation would result in higher risk estimates for spontaneous abortions and terminations than those enrolled later. Still, unless periodic pregnancy tests are conducted, studies will never pick up fetal losses that occur before pregnancy is known.

Women should be enrolled before the pregnancy outcome is known to avoid a selection into the study affected by the outcome. Retrospective enrollment of women after prenatal screening (i.e., nuchal translucency, chorionic villous sampling, amniocentesis, alpha fetoprotein measurements and second-trimester ultrasound (first trimester dating ultrasounds do not assess malformations)), whether the test is normal or abnormal, can introduce bias towards a lower or higher risk of malformations.[1] Underestimation of the risk might occur if enrollment after informative screening tests are conducted selects a survivor cohort of women with uneventful pregnancies (e.g., women might be less willing to contact a "pregnancy registry" after a major malformation diagnosis, clinicians enrolling patients might miss women who had a therapeutic abortion, and some registries do not allow enrollment of women with abnormal prenatal tests or pregnancy losses when an abnormality has been identified). Overestimation of the risk might occur if participation is allowed after an abnormal test and there is a preferential enrollment of women with a diagnosis (e.g., the diagnosis prompts the exposed woman to look for information, find the registry, and enroll). These two scenarios can coexist and even occur differentially in unexposed and exposed women, leading to spurious associations. For example, a reference group of unexposed women might be more willing to volunteer if they are enjoying an uneventful gestation, while women with chronic conditions (e.g., rheumatoid arthritis) might contact a pregnancy registry after receiving an adverse pregnancy diagnosis, seeking both personal support and contact with peers with the same medical condition. Because this bias is difficult to identify and correct in the analytic phase, it needs to be prevented in the design by enrolling subjects prospectively before the outcome is known.

6.2. Follow-up

Another peculiarity of pregnancy studies is that followup needs to go beyond the onset of the outcome under study. For most major structural congenital anomalies, the theoretical followup would be from conception to the end of fetal organogenesis (i.e., on average three gestational months). However, one often learns about the fetal outcomes only after birth. Longer followups will identify more congenital problems since some structural and many functional malformations might become clinically apparent

only months or years later. [19, 23] In pregnancy registries, followup typically stops at three to 12 months after the end of pregnancy. Some registries restrict the cohort to infants with a minimal standard followup time, such as at least three months after birth (of note, fetal deaths and infant deaths before the minimal followup should also be included in the assessment to avoid excluding lethal malformations). Efforts should be made to minimize losses to followup and to obtain outcome information for all participants. Information needs to be collected on the number of losses and, if possible, on their reasons, in order to assess whether they are similarly distributed among exposed and unexposed.

7. Exposure Ascertainment

How registries collect information can affect the accuracy of the data. Some registries obtain information from the woman herself. Women often know more about their habits, occupations, medical and obstetrical history, and compliance with the drug than individual health care providers. Other registries rely on reporting by the clinician and have no contact with the patient. Clinicians can provide more complete and accurate information regarding diagnoses and indications.[24] However, there is a risk of exposure misclassification if women stop or incompletely comply with the prescription drug regimen during pregnancy. A woman might be more willing to tell an interviewer not related to her care than to tell her doctor that she decided to reduce her dose or quit taking a medication. Including unexposed subjects in the exposed group (i.e., false positives) can dilute any potential association.

In order to maximize the quality of data, the combination of several sources of information is an optimal strategy. With adequate help, women can recall exposure during pregnancy. As noted previously, they should be enrolled before the pregnancy outcome is known to reduce selection bias, as well as to obtain reliable prospective information on exposure and other characteristics not affected by the outcome. One interview should take place at enrollment (i.e., during the first trimester), and at least one interview should take place post-partum (e.g., 2 months after end of pregnancy). Additional interviews (e.g., mid pregnancy to update exposure information, 12 months after delivery to evaluate development) might be useful depending on the objectives of the pregnancy registry. Data from treating physicians can document the medical condition and confirm the prescription. Confirmation of exposure should be blinded to the outcome.

8. Exposure Definition

If one were concerned about structural malformations, the etiologically relevant period of exposure would be the first trimester of pregnancy. To identify this period, one needs to establish gestational timing. Obstetricians typically time pregnancies from the first day of the last menstrual period (LMP), determined by maternal recall or, preferentially, by a more accurate early pregnancy ultrasound. Depending on the pharmacological characteristics of the drug, the specific defect, and the accuracy of timing information, the window of interest might be the second and/or third month, any time during first four months after the LMP, or even weeks before LMP for drugs with long half-lives or unspecified period of effect (e.g. vaccines). Exposures later in pregnancy can adversely affect other outcomes.[25-27]

Treatment strategies change during pregnancy, and doses are commonly adjusted. Therefore, it is recommended that detailed information on start and stop dates, dose, frequency, duration, and indication be collected.[28] Some medications (e.g., anticonvulsants) are prescribed in combination with other drugs. The effect of polytherapy resulting from concomitant treatments, or from switching drugs, within first trimester should be explored in the analyses. Not only the number of drugs, but which drugs are

combined, might affect the outcome of interest. Although the power is usually limited, analyses of dose response can inform recommendations, analyses of specific timing within first trimester can assess biological plausibility, and analyses of indications might help explore confounding. If possible, maternal body mass index should be considered when evaluating dose effects.

9. Covariates: What Else to Collect?

There is always a tension between simplicity and a desire to be comprehensive. Although there is no general rule, one widely accepted principle is that quality is more important than quantity (if the information is not trustworthy, do not collect it). Minimizing the effort and time from participants can increase both the willingness and the quality of participation. Necessary information on exposure, outcome, and key confounders (e.g., history, status, severity, and management of the indication) should take preference over desirable but less useful information. Most registries collect information on demographics, concomitant illnesses and medications, and reproductive history. A list of variables commonly collected in pregnancy studies is provided in Table 26.

Table 26. Variables Commonly Collected in Exposure Pregnancy Registries

Identification	Exposure	Outcome	Covariates
Study ID Date at enrollment LMP date or EDD gestational age at enrollment Date first data collection Date(s) of followup data collection(s) Date end of followup Follow-up status (e.g. complete, loss to followup, withdrawal) Contact information -Woman - Alternative contact(s) -Obstetrician / prenatal health care provider -Specialist -Pediatrician	Drug (for each drug, each episode of use and each dose if changed): -Start date -Stop date -Indication and measure of disease severity (e.g. CD4 count for HIV patients, type of epilepsy and convulsions during pregnancy for anticonvulsants) -Dose -Route -Frequency -Duration	Sex Status (livebirth, elective termination, spontaneous abortion, late fetal death) Number of fetuses (singleton or multiples) For fetal loss: Date end of pregnancy Reason for termination For Livebirth: Date of birth Birth weight Birth length Head circumference Gestational age at birth Conditions at birth (e.g. admission to intensive care unit, drug withdrawal syndrome) Congenital anomalies: Specific defects Date of diagnosis Methods of diagnosis Date and results of any prenatal testing Obstetric outcomes: Delivery (vaginal, C-section type)	Demographics: Maternal age, race, occupation, education level. Pre-pregnancy weight and height. Reproductive history: number of previous completed pregnancies and miscarriages, fertility interventions for past and current pregnancy. Family history of defects (specific defect and degree of relationship). Habits: cigarette smoking, alcohol intake, and use of illicit drugs. Chronic medical conditions: diabetes, pregravid obesity, hypertension, epilepsy, depression, other psychiatric disorders, hepatitis, thyroid disease, autoimmune disease, asthma, sexual transmitted disorders, AIDS.

		Preeclampsia Premature labor Preterm delivery Gestational diabetes	Concomitant medications including folic acid supplementation and potential teratogens.

NOTE: LMP: Last menstrual period. EDD: Estimated date of delivery

10. Outcome Ascertainment

The source of information for outcomes in pregnancy registries is critical. Although registry designs that incorporate interviews with pregnant women can provide an initial source of data regarding the results of prenatal diagnosis, postnatal events, and malformations that are recognized during longer term followup periods, validation of any maternally-reported diagnosis by the health care provider is an important criterion for inclusion of specific outcomes such as major congenital anomalies in most registries (see Outcomes Definitions below). In registries where the outcome is routinely collected from the woman and validated with health care providers, the mother's report can correct potential false negative reports from one clinician; in comparison, registries where the outcomes are only reported by the provider rarely include maternal validation. In some circumstances, a more stringent level of validation might be required to confirm an outcome (e.g., an echocardiogram to validate the presence of specific heart defects). Requiring commitment at enrollment to provide consent and medical release of information from obstetrician and specialists might select a motivated patient population and can minimize loss to followup and maximize access to medical data.[2]

Whether the exposure is ascertained from the patient or from the clinician, it is important to obtain delivery data from the obstetrician or hospitalization records to ascertain the outcome accurately. It is also important to followup with subsequent providers, such as the infant's pediatrician and other specialists, because those treating a woman for a non-pregnancy related condition often know little about obstetric or pediatric outcomes (e.g., a woman's neurologist might not know about the patient's preeclampsia), and obstetricians often know little about the infant after delivery.[1, 19] Obtaining this information might require woman's consent and therefore contact with the patient. In addition, treating physicians might have a legal or ethical conflict of interest if they are asked to report on pregnancy outcome when they were responsible for the exposure.

It is important to recognize that maternal report alone can result in misclassification of the presence or absence or any defect and/or the presence or absence of a specific defect. Although specificity is most relevant for the evaluation of infrequent outcomes, medical validation may be required for all births and not just those in which the mother reports an abnormality to maximize sensitivity.

Other primary or supplemental methods of ascertainment of birth defect outcomes can be employed. These include linkage to claims data, public birth registries, or birth defects surveillance systems. In any case, comparable methods for ascertainment of outcomes must be used in the exposed and reference groups.

11. Outcome(s) Definition

Pregnancy registries must set *a priori* criteria for defining outcomes as part of the study design. Outcomes are typically ranked in order of importance to the registry objectives. For example, most pregnancy registries select major structural birth defects as the "primary" outcome of interest. This outcome is frequently defined as primary because identification of an increase in major malformations, particularly specific major malformations, in association with a given gestational exposure may indicate a teratogenic effect. In addition, some pregnancy registries incorporate a measure of "minor" structural defects as an outcome representing a broader spectrum of potential structural differences that may be attributable to an exposure.

Other "secondary" endpoints frequently include measures of fetal growth deficiency, preterm delivery, spontaneous abortion or stillbirth, and elective terminations. Some pregnancy registries incorporate longer-term measures of outcomes that can include, for example, postnatal growth deficiency, cognitive and behavioral development, or measures of immune function, depending on the characteristics of the exposure under study in the registry. However, the cost and logistics of following children over time usually are prohibitive.

Using the primary outcome of major structural defects as an example, but relevant to all outcomes in any pregnancy registry, the following definitions must be determined *a priori*.

11.1. Inclusion / Exclusion Criteria for a Defect to be Defined as "Major"

Criteria for defining defects as "major" must be established for a pregnancy registry. For example, major structural defects might be defined as abnormalities in structural development that are medically or cosmetically significant, are present at birth, and persist in postnatal life unless or until repaired. Similarly, criteria must be established for defects that will be excluded. For example, those that are transient and maturational such as a patent ductus arteriosus or an inguinal hernia that might occur in a preterm infant simply as an artifact of shortened gestational age but do not represent an abnormality in embryonic or fetal development might be excluded. Another example of an excluded defect might be a small muscular ventricular septal defect that may spontaneously close with no consequences for the infant. Attention must be paid to the comparability of definitions for inclusion and exclusion between the exposed and the reference groups.

Frequently, pregnancy registries employ an existing standard coding system for inclusion and exclusion of structural defects, such as that developed by the U.S. Centers for Disease Control and Prevention's (CDC) Metropolitan Atlanta Congenital Defects program.[29] This system was created and is maintained for use in an ongoing population-based surveillance program for birth defects that are identifiable up to one year of age. For some pregnancy registries, additional definitions or modified inclusionary/exclusionary criteria may need to be employed, depending on the length of followup or the specific outcomes of interest. Even with standard coding criteria, the information available for some defects that are reported may be insufficient or ambiguous for classification such that an additional level of review is required to classify the defect appropriately. A method for expert adjudication of defect classification, blinded to exposure status, is an important component of a pregnancy registry.

Minor malformations are defined as those uncommon structural differences in the infant that have no serious medical or cosmetic consequences (e.g., an extra hair whorl on the head). Although these minor structural defects are of potential interest as more subtle measures of outcome, they may not be reliably

assessed and therefore are frequently excluded unless they are uniformly evaluated in all patients. Similarly, positional deformities are often excluded (e.g., abnormal head shape or plagiocephaly that spontaneously resolves shortly after birth).

The source of information regarding a major structural defect must also be defined as meeting the criteria for inclusion. For example, maternal report of a malformation with no validation by a physician or postnatal diagnostic test may be defined as insufficient for inclusion of a major defect. Another example of a situation that might be defined as exclusionary is a defect that is suggested through prenatal diagnostic tests but for which no postnatal validation is available.

11.2. Timeframe of Diagnosis

A specified period for followup through which standardized efforts to collect outcome information on major birth defects should be determined as part of the pregnancy registry design. As length of followup increases, the baseline risk of major structural defects is expected to increase because not all structural defects are reliably recognized at birth. Ideally, the longer the followup, the more complete an assessment of major birth defects could be. Specific outcomes of interest for the exposure under study may require longer followup to be appropriately assessed. However, the length of followup selected for the registry may be influenced by the availability of resources and ability to maintain contact with registry participants and/or health care providers over a longer term. For comparability reasons, it is essential that the timeframe for diagnosis be identical in the exposed and the reference population or group.

In addition, the case of major birth defects that occur in pregnancies that end in embryonic or fetal demise must be considered in the registry design. Major defects might be identified in spontaneous pregnancy losses by post-natal pathology, and criteria for inclusion of those defects must be established, as not all spontaneously aborted pregnancies or stillbirths will be uniformly evaluated for the presence or absence of defects. In the special case of elective terminations, criteria for ascertainment of malformations are critical because terminations for defects that are identified on prenatal diagnosis may represent an important subset of outcomes within the registry. Elective terminations for social reasons may not be uniformly evaluated by prenatal diagnosis for major structural defects. For these reasons, many pregnancy registries treat malformations identified in pregnancies ending in live birth separately from malformations included in the overall sample of registry pregnancies including terminations, spontaneous abortions and stillbirths. Failure to include defects detected among terminations can decrease power and introduce bias, particularly for defects for which termination is often chosen after prenatal diagnosis (e.g., neural tube defects).

11.3. Analytical Approach

No known teratogen increases the risk of all major birth defects. Typically, a specific defect or pattern of defects occurs with increasing frequency following a teratogenic exposure in the critical gestational window for susceptibility. However, specific major defects are rare events in the general population – the most common occur no more frequently than ~1 in 1,000 live births. Pregnancy registries usually do not have sufficient sample size/power to evaluate increased risks for specific defects unless the relative risks are quite large. Therefore, most registries compare the overall proportion of all major defects combined in the exposed group to the overall proportion in the reference group. The rationale for this approach is that if specific defects are increased following exposure, these specific defects will incrementally inflate the overall proportion of malformations in the exposed sample and therefore reflect the excess risk

associated with that exposure. For example, if the baseline risk of major malformations is 3% and the risk of neural tube defects is 0.1%, a five-fold increased risk of neural tube defects would inflate the overall risk to about 3.4%. Although the analytic approach for a registry may be based on a comparison of all malformations combined, it is important for pregnancy registries to evaluate any potential excess of specific defects in the exposed group, even if it is descriptive.

In some registry designs, it is argued that malformations of known etiology should be excluded from the overall proportion of major structural defects as they do not have the potential to have been "caused" by the exposure. Examples might be chromosomal anomalies, those defects that have a known single gene cause, or occur in families with a positive history for that defect. The rationale for these exclusions is that inclusion of defects not thought to be caused by teratogens can decrease power to detect an overall difference in risk between exposed and unexposed fetuses. Arguments against exclusion of such defects in the analysis are that the true cause of the defect may not be known and that it is possible that exposure to a medication modifies other risks for that defect in a multifactorial manner. Therefore, by excluding such defects one could miss the effect.[30] Inclusion or exclusion of chromosomal defects or those of other known etiology may also be driven by the inclusion or exclusion of those defects in the reference population that is selected for comparison.

12. Reference Group(s): Internal or External, Exposed or Unexposed?

A critical element for pregnancy exposure registries is the choice of comparator groups. A valid reference group needs to have comparable 1) outcome definition (e.g., exclusion of minor anomalies); 2) outcome assessment (e.g., intensity of screening, frequency of terminations, inclusion of prenatal diagnoses, availability of diagnostic tests, start and stop of followup);[23] 3) selection of subjects into the study (e.g., gestational age at enrollment); and 4) baseline risk (e.g., distribution of risk factors, including indication). Ideally, each registry is constructed to include an internal reference group. When this is not possible, inclusion of an external reference group must be selected with care. Each comparison group has its advantages and disadvantages. For example, an external population-based reference can provide stable estimates for specific malformations, while internal comparison group would have limited sample size to asses specific malformations but can provide more comparable estimates for malformations overall. More than one comparison group can be contemplated in the protocol to improve the overall validity and statistical power. In anticipation of potential conflicting results, however, primary comparison groups should be identified and justified *a priori*.

External comparators are usually considered less valid than internal comparators; for example, a RCT or observational study on the relative risk of stroke in an elderly population exposed to a drug would never use an external reference. However, pregnancy registries often compare their estimates with the background risk in "standard populations" such as the CDC's Metropolitan Atlanta Congenital Defects Program, where the frequency of malformations among pregnancies of 20 weeks or greater is 2.1% when diagnosed prenatally or within the first week of life, and 2.6% if infants are followed until the first birthday;[19, 23] or EUROCAT data in Europe where the prevalence at birth is 2.0%.[31] One advantage of the use of available data from large external reference populations is that it avoids the costs in time and money of enrolling unexposed subjects and provides stable risk estimates for common specific malformations in the general population.

External reference groups must be used with caution since the estimated risk of "major malformations" can vary widely depending on the population, on the definition, and on the ascertainment methodology. When external references are the only alternative, they must be appropriate to the population being studied. Analyses should at least take into account the characteristics of the surveillance program and use the same methodology in their exposed group. For example, characteristics to be considered are whether prenatal diagnoses and terminations were counted, were malformations identified during the delivery hospitalization or was there followup for a number of months, or were chromosomal malformations and minor malformations included. Many registries use external references as a necessity. Information from these sources can be helpful, particularly when there are no other data available, and as long as findings are interpreted with caution. For example, external references can identify major teratogens (like thalidomide), generate hypotheses when unusual patterns of malformations are identified, and inform the need for additional, targeted, epidemiologic studies.[24]

Some registries enroll an internal reference group of unexposed women who undergo the same processes as the exposed and then adjust for potential confounding by matching or adjusting for key covariates. There is still some risk of differential gestational time at enrollment (exposed women may tend to enroll earlier) and lack of comparability (unexposed women rarely have the underlying condition for which the drug was indicated). To make groups more comparable, some registries use women exposed to other non-teratogenic drugs as the reference (e.g., OTIS registries)[32] or enroll pregnant women with a common condition or indication treated with various drugs or untreated (e.g., the multi-sponsor North American Antiepileptic Drug [NAAED] Pregnancy Registry,[33] and the human immunodeficiency virus [HIV] Anti-retroviral Pregnancy Registry[34]). More recently, the scientific community has moved towards the evaluation of the comparative safety and efficacy of different treatments with similar indications used in similar populations, whenever possible. The comparability of groups is enhanced by this approach, although sometimes more severe conditions are channeled to specific treatment, while milder ones can remain untreated, thus confounding by severity or type of disease is still possible. In addition to improving validity, using alternative treatments as a reference would answer the clinically relevant question of "how to treat" rather than whether to treat. Moreover, since there is often need for safety data for multiple drugs with the same indication, evaluation of a variety of drugs used to treat the same condition could be most efficient. The feasibility of multiple-drug registries depends in part on the sponsorship.

Taking advantage of the etiologically relevant periods of exposure during pregnancy, some studies compare first trimester with second or third trimester use of the drug. These comparisons are only possible for non-chronic treatments and should consider that the opportunity for exposure after first trimester can be affected by the outcome. For example, if the pregnancy is terminated because of a malformation, there would not be second/third trimesters exposures; therefore, later exposures might be artificially associated with lower risks.

13. Analysis of Registry Data

Pregnancy registries frequently include multiple outcomes as endpoints and may have more than one comparison group; in addition, as stated above, major birth defects among live births may be evaluated separately from major birth defects among all pregnancies. To address the problem of multiple comparisons in analysis and interpretation of registry data, it is essential to establish an analysis plan that

identifies the primary hypothesis being tested, typically the proportion of pregnancies involving a major birth defect, and to specify which are the primary groups being compared.

Similarly, the analysis plan should attend to the design of the registry and the expected sample size. For example, registries that involve multiple centers/multiple countries should use appropriate conditional methods of analysis that account for center. For outcomes with low frequencies, e.g., major structural defects, sample size projections should indicate when exact methods must be used for analysis. To evaluate the robustness of findings in the registry, the analysis plan can incorporate a plan for *post-hoc* sensitivity analyses under various scenarios.

14. Statistical Power, Registry Size, and Duration

The projected sample size for a specific pregnancy registry is affected by the frequency with which the medication is used by women of reproductive age, the proportion of exposed pregnancies that it is estimated are possible to identify and recruit into the registry, and the scope of the registry (local, national, international). The power of the study to detect an effect at or above a certain level is affected by the sample size and the baseline risk for the outcome in the population.[19] The estimated losses to followup will affect the useful sample size. The duration of followup for outcome assessment will affect the cumulative risk estimate. Missing therapeutic abortions will affect both.

If the medication under study typically is only taken for a few days or intermittently, this fact should be considered in calculations of power and sample size. The effective sample size of pregnancies exposed only in specific gestational windows of time (any one of which may be a risk period while others are not) may be much smaller than the overall projected sample size of pregnancies exposed for the registry. These factors must be balanced against the amount of time needed to accumulate a sample size that is sufficient to produce a clinically relevant result.

For example, in a pregnancy registry that compares the overall proportion of pregnancies resulting in an infant with a major birth defect among exposed women to an external reference population with a baseline prevalence of major defects of 3%, a sample size of 200 exposed live born infants would be sufficient to detect a 2.2 fold relative risk with 80% power at an alpha of 0.05. However, the same sample size of exposed live births would only be sufficient to detect a 10.4 or greater relative risk for cleft lip with or without cleft palate.[34]

Because of the limits of power associated with typical sample sizes for pregnancy registries, especially in detecting risks for specific birth defects, an approach that has been used in some registries is the "rule of three": an alert is triggered when three or more specific defects are reported for a specific exposure. This rule is based on the <5% likelihood of a chance finding of three or more of the same specific, relatively rare, defect in a cohort of 600 or fewer subjects. Although some defects or defect groups occur frequently enough that the "rule of three" would not apply, this method can be used to flag an unusual finding for further review.[34]

15. Biases

15.1. Selection Biases

Because pregnancy registries typically enroll women only after recognition of pregnancy and in some cases much later in pregnancy, the group of enrollees is a selective group of pregnancies that have

survived to that point in gestation and may have a shortened remaining period at risk of incurring the outcome of interest. There is "left truncation" of the registry cohort such that it is devoid of women who have already had a spontaneous abortion, an elective termination, or a stillbirth depending on the gestational age of enrollment. Although statistical methods can be used to address left-truncation, survivor bias threatens ability to evaluate risk for pregnancy outcomes including birth defects and calls for a registry design that encourages recruitment of participants as early in gestation as possible. In the extreme, one cannot study infertility in a cohort of pregnancies because, by definition, women conceived. Nor would one estimate the incidence of spontaneous abortions in women enrolled after 20 weeks of pregnancy. Spontaneous abortions can still be evaluated when women are enrolled during the first trimester by assessing the rate of miscarriages per gestational month, thus taking into account the decreasing trend as gestation progresses and the gestational time at enrollment.

Early enrollment is also of benefit with respect to biases potentially introduced by prenatal diagnosis. Prospective registry enrollment before any prenatal diagnostic test for major birth defect avoids bias in the direction of an increased risk for defects so identified, or in the other direction if women enroll preferentially after prenatal diagnosis that has shown no defect. Pregnancy registry guidelines recommend that only participants enrolled prior to prenatal screening be included.[2] However, as prenatal diagnosis becomes feasible earlier in gestation, this becomes more difficult to achieve.

Many registries also collect data retrospectively, but these data should be analyzed separately. Women enrolled after an abnormal pregnancy test can be analyzed as case series in passive surveillance systems of spontaneous adverse event reports.[2] Malformations can be evaluated for biological plausibility, and specific patterns of malformations or distinct congenital abnormalities can generate hypotheses. On the other hand, retrospectively enrolled subjects without malformations would offer limited information, therefore, the benefit (and ethics) of including these women is questionable.

Registries should report the gestational age at enrollment for their exposed and reference groups. If enrollment time differs, methods that adjust for left censoring such as restriction to prospective pre-tests enrollees should be applied.

Another bias might be associated with right truncation of the registry cohort. This occurs when pregnancies with unknown outcomes are considered ineligible for analyses. By excluding terminations, spontaneous abortion and losses to followup, one assumes that the exposure had the same effect in these pregnancies as in those that remain under observation. Such assumption is less plausible if the exposed group has a higher frequency of these outcomes than the reference group. The frequency of spontaneous and therapeutic abortions, losses to followup, and withdrawals should be reported for the exposed and reference groups. Of note, a higher frequency of terminations among exposed women might reflect a higher risk of malformations, as well as more fear of malformations with consequent abortion if the drug is suspected of being teratogenic.

Bias may also occur with events that shorten the followup (e.g., preterm delivery that cuts the possible number of weeks of exposure to the drug of interest). The assessment of transient exposures (e.g., vaccines) during pregnancy in relation to outcomes associated with shorter gestations (e.g., preeclampsia, prematurity, pregnancy weight gain) needs to take into account the smaller opportunity for exposure in shorter pregnancies.

Biases can also be introduced in the analysis by stratification or adjustment for covariates that are themselves affected by the exposure of interest and are affected by the outcome or share common causes with the outcome (e.g., adjusting for gestational age at birth when studying the effect of a pharmaceutical on structural malformations).[35-37]

15.2. Information Bias

As noted above, pregnancy registries are preferentially "prospective" in design. Therefore, the outcome cannot directly affect the accuracy of exposure information, and any misclassification of drug exposure would tend to be non-differential with respect to the outcome. However, non-differential misclassification of exposure is still problematic for safety evaluation since it would tend to bias any potential effect towards the null. It is therefore crucial to maximize the quality of drug exposure information.

When information on exposure is provided by the women, the accuracy of the recall can be maximized by using structured questionnaires, detailed questions, and calendars to help establish gestational timing and enhance recall of dates. Maternal reports on drug utilization are sometimes cross validated with medical records. When the health care provider is the only source of data, information on prescriptions might not reflect the real use of the drug during pregnancy if patient compliance is incomplete. Since pregnancy registries typically focus on uncommonly used medications, the impact of false positives among exposed is much greater than the occasional inclusion of false negatives among the unexposed reference group.

At the time of enrollment in the registry, women are reporting their medical history retrospectively, knowing that they are enrolled in the registry because there is lack of information on the safety of the drug under study. This potentially could influence the accuracy of recall for baseline covariates (i.e., recall might be more accurate for exposed than for unexposed groups because there is a different motivation to recall a medical history) and affect the ability to control for confounding. For this reason, methods for validation of key covariates are of benefit.

Diagnostic bias, or outcome misclassification, could also occur in pregnancy registries. These biases could be either non-differential or differential between the exposed and the reference group and could bias the estimate of an effect towards or away from the null. For example, participation in the registry itself or concern that a drug exposure might pose a risk could lead to more access to or uptake of prenatal diagnostic measures such as ultrasound and to more careful examination of infants for defects postnatally, potentially leading to differential accuracy in detection and classification of defects among exposed and unexposed. The risk of differential outcome classification among the exposed and the reference is greatest when external control reference groups are used.

As mentioned above, reported major malformations must be validated. Although neither treating physicians nor women are blinded to the treatment, registries can do blinded validation and adjudication of outcomes. To detect malformations not reported by the patients, records for all pregnancies would have to be reviewed. For example, women might be less likely to volunteer information regarding male genital malformations in their infants, which could result in under-ascertainment of these malformations. To detect malformations detected by screening and frequently terminated (e.g., anencephaly), therapeutic abortions need to be included. To detect an increase in abnormalities incompatible with life, it is important to collect information on autopsy results at stillbirth and, if possible, on examinations of the fetus after spontaneous or induced abortion. The study of spontaneous abortions and pregnancy

terminations itself presents an additional methodological challenge, especially in countries where abortions are illegal or when studies include pediatric populations, because induced fetal losses are sometimes categorized as spontaneous in medical records, and questions about terminations might be considered of sensitive nature.

15.3. Confounding

Several sources of confounding may affect pregnancy registries, as in any other observational study. Socioeconomic status, maternal age, tobacco and alcohol use, illegal drug use, maternal body mass index, vitamin use are examples of potential confounders that might be related to, or impact, the exposure under study and are also risk factors for some pregnancy outcomes.

With medications, there is the concern of confounding by indication (e.g., the association of a weight loss drug with birth defects might be confounded by the maternal obesity the drug is used to treat). Confounding by indication is difficult to address in non-randomized studies for common chronic conditions such as depression, asthma, epilepsy, HIV, and autoimmune diseases where separating the effect, if any, of the drug from the underlying disease can be challenging. A related form of confounding that may be of concern is channeling bias (i.e., women with more severe underlying disease may be most likely to be selected to receive the drug of interest).

Each of these potential confounding concerns provides a strong rationale for inclusion of actively recruited comparison groups that are matched to the exposed registry participants on the maternal underlying disease and, to the extent possible, similar in distribution of maternal disease severity.

16. External Validity or Generalizability

As mentioned above, pregnancy registries typically rely on volunteers to participate. With appropriate selection of comparison groups and control for sources of confounding, pregnancy registries can make assertions about internal validity. However, there is usually little known about the characteristics of the entire population of exposed pregnant women from whom the sample is drawn. For this reason, it is difficult to make conclusions about external validity or generalizability for any pregnancy registry. If the participants represent a select group, it may be difficult to generalize the findings from the registry. However, the registry volunteers would have to differ from non-participants on some characteristic that modifies the effect of the drug on the pregnancy outcome (e.g. a teratogenic effect might vary by race or by baseline folate levels in the population).

17. Operations

17.1. Study Protocol

Pregnancy registries are scientifically rigorous studies designed to monitor safety of product use in pregnancy. As such, they have formal written protocols based on epidemiologic principles and regulatory authority guidance documents for pregnancy registries.[2, 5] The protocol should include a brief and cogent review of the literature, registry objectives, study design, detailed data collection procedures including sources of data, inclusion and exclusion criteria for patient enrollment, operational aspects of enrollment and retention, definitions of relevant endpoints, analytic considerations, statistical plan, regulatory and ethical considerations, reporting and publication plans, governance, and criteria for registry termination. While protocols of RCTs are registered (e.g., on ClinicalTrials.gov), it is still controversial whether those from observational studies should also be registered.[38]

Pregnancy registries have procedural differences that are distinct from RCTs and from other observational study designs. Thus, they often require specific standard operating procedures that clearly document their unique processes. Each pregnancy registry should also have its own registry management plan that serves as the registry team's roadmap to conducting the registry. For more details see Chapter 2.10.

17.2. Human Subjects, Informed Consents, and Medical Records Release Forms

Pregnancy registries involve human subjects research and thus involve institutional review board approval, informed consent of participants, and protection of confidentiality in data collection, data storage, and publication. Pregnant women are considered a 'vulnerable' population in legal/ethical terms but, importantly, unlike other populations considered in this section of regulations (mentally challenged patients, inmates in penal institutions and children), they are able to give consent. Therefore, registries must adhere to guidelines for human research protection in pregnant women. Pregnancy registries are typically considered minimal risk protocols. As with participation in any research of this type, there is the potential for loss of the confidentiality of the information provided. Methods to manage this risk must be in place and communicated to the potential participant. There is also the psychological risk of participation in a pregnancy registry that may be involved when a woman becomes more aware of the potential fetal effects of exposure. Resources for expert counseling on fetal risks are available in the U.S. and Canada through the Organization of Teratology Information Specialists (http:www.otispregnancy.org).

Informed consent is typically required for participation in a pregnancy registry. Some registries collect data directly from health care providers without collecting patient identifiers. These types of registries may qualify for a waiver of informed consent. For pregnancy registries in which the patient is identified and data are collected from multiple sources, informed consent is required. However, under several conditions, signed informed consent may be waived and verbal consent allowed. Additionally, in order for pregnancy registries to collect data from a woman's health care provider(s) and/or her newborn's pediatric health care provider, the woman must complete medical release forms for each clinician who will report data or provide medical records to the registry. Chapter 7 thoroughly discusses the application of ethical principles for registries.

17.3. Recruitment and Enrollment

In some registries, pregnant women self-identify and self-enroll calling a toll-free number that can be found in key websites, printed materials in specialists' offices, or drug inserts. In other registries, women are referred by general practitioners, specialists treating the condition of interest, or obstetricians. Direct enrollment of women may allow inclusion of participants earlier in gestation since they are usually the first to know about their pregnancy. Enrolling women directly may also facilitate pregnancy and postnatal followup. However, for some drugs, it might be unrealistic to expect self-enrollment and, for some conditions, it might be more efficient to identify eligible women through specialists. Some countries do not allow self-enrollment. Who initiates enrollment has implications for data collection and informed consent processes.

Pregnancy registries can be conducted by regulatory or other government agencies, academic centers, contract research organizations (CRO), or drug manufacturers. Who sponsors and who conducts the registry can affect the participation of health care centers, some of which might have barriers for collaborations with industry. Biopharmaceutical companies sometimes identify exposed pregnancies as

outcomes reported to their surveillance system for drugs not recommended for pregnant women. If identified and enrolled before prenatal tests, these pregnancies can be followed and yield a pregnancy registry nested in a passive surveillance system.

To maximize enrollment and maintain efficiency, pregnancy registries typically do not use a traditional "site-based" approach. Rather they employ a single coordinating center that recruits and enrolls all eligible pregnant women as soon as possible after conception. The number of coordinating centers that would make the study feasible varies among countries and among registries. Therefore, awareness campaigns must reach out to pregnant women and their health care providers in a broad variety of settings. A carefully constructed awareness plan should be designed specifically for each pregnancy registry, accounting for the aims of the registry, the target population, and the geographic scope. In general, the plan should incorporate a variety of persistent awareness strategies to ensure broad coverage, including announcements of the registry with contact information posted in the following:

- Product label
- Registry and/or product Internet sites
- Personal mailings to health care specialists – particularly high prescribers and high-risk obstetricians
- Professional journals
- Exhibits or scientific presentations at professional meetings
- Lay magazines
- Advocacy group newsletters and/or Internet sites
- Social media

For pregnancy registries sponsored by individual biopharmaceutical companies, promotional materials are subject to 21 CFR 314.81(b)(3) or 601.12(f)(4), and should be submitted to the FDA Division of Drug Marketing, Advertising, and Communications (DDMAC). In general, registry recruitment and awareness materials should not promote use of the product in pregnancy nor imply that the product is safe and effective in pregnancy unless sufficient scientific evidence exists to support these claims.

Enrollment might also be affected by the lag time between approval of the pharmaceutical and launching of the registry. Awareness and interest might peak right after approval, which is also the ideal time to collect safety data in the post-marketing setting. Streamlined procedures for informed consent and data privacy/HIPAA authorization have been demonstrated to increase enrollment in pregnancy registries.[39]

17.4. Retention of Participants during Follow-up

Participant retention is crucial to achieving the registry goals. Retention can be encouraged by engaging registry participants, including pregnant women and their health care providers in the reporting process and making it as easy as possible to report data to the registry. Registry staff should be trained to collect data for observational studies from both patients and health care providers who do not usually participate in research activities. They should develop a rapport with the reporters that facilitates data collection and promotes retention through relationship building.

Streamlined data collection processes and simple, concise data collection forms are essential for reducing the burden of reporting. For registries sponsored by pharmaceutical companies, duplication of work because of safety reporting should be avoided as much as possible. A small monetary stipend may also

encourage retention but may not be universally accepted by registry reporters. For health care providers, especially obstetric care providers, registry data are often more valuable than a stipend. Giving interim data reports to health care providers who report data to the registry is a powerful recruitment and retention incentive.

17.5. Data Collection

Like any other epidemiologic study, registries can benefit from the technologic advances in communications (e.g., ability to enroll subjects through social networks and collect data through confidential websites). Most registries enter the data directly into an electronic database from records or questionnaires, or using computer-assisted telephone interviews. To assure confidentiality, identifiers should not be included in the database containing clinical information. The goal is to make reporting data to the pregnancy registry as easy and unobtrusive as possible. Providing a variety of data-reporting mechanisms that are simple to use and fit the reporters' preferred communication practices facilitates recruitment and retention. If feasible, a pregnancy registry should be designed to allow participants to report data through telephone interviews, paper data collection forms that can be mailed, scanned, or faxed to the registry, simple Internet-based electronic data capture systems, and mobile applications. For details on these data capture systems, see Chapter 11.2.3.

Pregnant women are ideally enrolled into a pregnancy registry before or soon after the exposure of interest and then followed throughout pregnancy. If a live infant is born, the infant may be followed for a period typically ranging from 3 to 12 months. Data may be collected at several different time points.

- At enrollment, information is collected on product exposure(s), maternal characteristics, prenatal testing, and other baseline data.
- During the second and/or third trimester of pregnancy, a brief update on the status of the pregnancy and exposures may be obtained.
- At end of pregnancy, information is collected on additional exposures during pregnancy, risk factors, and details regarding the pregnancy outcome, including any congenital anomalies, gestational age and birth weight, and perinatal complications.
- For live births, data may be collected at several points in time (typically 3, 6, and/or 12 months) on infant characteristics and health outcomes including congenital anomalies, functional or developmental deficits, and other outcomes pertinent for the drug of interest.
- Targeted followup may be needed to collect additional detailed data on specific outcomes of interest.

The source of baseline and followup data is an important consideration. It is best to evaluate all options for obtaining data to determine the most appropriate source for the specific data requested. The pregnant woman can provide detailed data on drug use including exposures to the drug of interest as well as other drugs, on relevant risk factors, and on the pregnancy outcome. Her health care providers, such as the prescriber, specialists and/or obstetrician should be able to provide or verify this information. The collection of data from a variety of sources throughout pregnancy and during infancy contributes to the accuracy and comprehensiveness of pregnancy registry data. Requiring information from multiple health care providers, in addition to the patient, is a distinct challenge of pregnancy registries.

Data quality is of the utmost importance in a pregnancy registry, and multiple levels of quality assurance should be employed beginning with the design of data collection instruments. Instruments should be designed with care, thoroughly vetted, and pilot tested to ensure ease of reporting valid, reliable data. Instructions for self-reporting should be clear and succinct. Electronic data collection (EDC) systems should include validity checks. If interviews are to be used, the interviewers should be thoroughly trained to conduct neutral, unbiased interviews using detailed interview scripts. Once captured, the data should go through a rigorous cleaning and quality assurance process to reduce errors, missing data, and misclassifications. When possible, patient-reported data should be verified by health care providers or medical records.

17.6. Adjudication of Outcomes

Many pregnancy registries enlist the services of a clinical geneticist or dysmorphologist to review and classify all congenital anomalies. A standardized classification system should be used, such as the Centers for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects program.[29] The assessor and method of assessment should be the same for both the exposed group and comparison group and the assessor should be blinded to the exposure of interest. The assessor may also evaluate likely causes for the particular birth defect, such as family history, genetic factors, and/or exposure to known teratogens.[28] If the exposure of interest is made available, the assessor may examine the timing of the exposure relative to the origin of the birth defect (e.g., to attempt to determine if the timing of the exposure is relevant to the formation of the birth defect).[28] Registries can engage the Scientific Advisory Board and/or a subgroup of the Board to review each case and the assessor's classification and reach consensus on the classification.

17.7. Process of Releasing Findings

17.7.1. To Regulatory Agencies

The FDA considers individual case reports from a pregnancy registry as derived from active solicitation of patient information (FDA 1997), including reports from participants enrolled both prospectively, where the exposure is reported prior to knowledge of the pregnancy outcome, and retrospectively, where the pregnancy outcome is already known at the time the exposure is reported.[2] A company sponsor holding marketing authorization for an approved drug or licensed biological product must submit to the FDA, within 15 calendar days, reports of pregnancy registry adverse events that are both *serious* and *unexpected* by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event. Current reporting requirements in the regulations consider any congenital anomaly a serious adverse event.

Pregnancy registries run independently of any sponsors holding marketing authorizations are not subject to postmarketing regulatory reporting requirements. However, investigators running such registries may forward reports of any serious adverse events including congenital anomalies to the sponsor of the medical product or report directly to the FDA MedWatch office (1-800-FDA-1088 or http://www.fda.gov/medwatch).

Any company conducting a pregnancy registry required by the FDA must submit an annual status report to the agency. Companies conducting pregnancy registries not subject to annual reporting requirements are encouraged to include a status report in the periodic safety report. The status/interim report should describe the study design and summarize the status of the planned, initiated, in progress, or completed

pregnancy registry conducted by or otherwise obtained by the sponsor during the reporting period. The status report should also provide a descriptive summary of progress to date, interpretation of findings and appropriate analyses with comments on the clinical significance of the findings. Copies of full reports may be appended, if appropriate. Any publications based on data from the registry should be included.

The registry status report should include the following, presented separately for prospective and retrospective reports: number of pregnant women enrolled to date, number of pregnancies with outcome known (stratified by live birth, spontaneous abortions, elective terminations, fetal deaths/stillbirths), number of pregnancies with outcome pending, and the number of pregnancies lost to followup (p 16, FDA guidance).[2] For pregnancies with known outcomes, line listings and summaries of: demographics, obstetrical, and medical history of mothers, weeks of gestational age at exposure, dose and duration of exposure, whether multiple gestation, and weeks of gestational age at completion or termination of pregnancy. For live births and deaths/stillbirths, small for gestational age, preterm delivery, and congenital anomalies or other fetal abnormalities, and for spontaneous abortions and elective terminations, abnormalities in products of conception, if known.

17.7.2. Reporting to Sponsors

There are no specific rules around reporting events to the sponsor company. The sponsor company negotiates this with the academic center or CRO. Some pregnancy registries have regular (semi-annual or annual) data cut-off points and issue corresponding periodic interim reports summarizing the aggregate data. The sponsor can then use this interim report for any regulatory reporting requirements.[1] Others, such as the NAAED have pre-specified criteria for release of results for a positive association.[33]

Most pregnancy registries administered by CRO or academic institutions report all adverse pregnancy outcomes (birth defects, spontaneous fetal losses, induced abortions), maternal and non-defect fetal events, regardless of attribution or seriousness, to the sponsor within a few business days. Some sponsors only request specific outcomes, or serious and attributable events, reported to them. The sponsor reports these events to regulatory agencies. Pregnancy is not considered an adverse event (AE). The registry might also report spontaneous AEs (not registry related outcomes) to the sponsor, although these may be received infrequently. If the sponsor requires further information on a pregnancy related AE, they can contact the registry who would contact the health care provider. The sponsor follows up on any non-registry cases as needed.

17.7.3. Publication Policy

Some pregnancy registries have formal publication committees.[34] In others, such as the NAAED, the investigators review plans to publish registry data and conclusions with the independent Scientific Advisory Committee, and a consensus to publish is developed.[33] Others simply publish the findings when they have them. Registry results should be published as soon as the number of women in the registry permits to allow dissemination of the results to the scientific and clinical communities.

17.8. Role of (Scientific) Advisory Board

The scientific conduct and analysis of the Registry are usually overseen by an independent Scientific Advisory Committee. The committee can advise and participate in establishing a registry and its design, as well as assist in the review of data, classification of any birth defects and the dissemination of information to ensure that results are interpreted and reported accurately. The role and duties of the committee should be specified in the protocol. Members of the committee could include experts in

obstetrics, embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, any relevant therapeutic areas and consumers representing the disease state being treated and may include members from the CDC, the National Institutes of Health (NIH), academia and the private sector. The Advisory Committee might review the Registry data, develop Consensus Statements, provide recommendations on modifications or enhancements to the Registry, and/or assist in the dissemination of information and formulation of strategies to encourage enrollment in the Registry. In addition to the Scientific Advisory Committee, multi-company sponsored pregnancy registries may also include a Steering Committee composed of representatives of the sponsoring pharmaceutical companies.

17.9. Stopping Rules

The criteria to determine when to end the study may be predetermined and specified in the protocol. If the registry is conducted by a drug company as a regulatory requirement then the decision as to when to actually end the study is made jointly by the company and the regulatory authority. In other pregnancy registries, it is the Scientific Advisory Committee that decides or contributes to the decision about when to stop. Sometimes, findings from the registry might affect the decision of whether it should continue.

Criteria for possible discontinuation of a pregnancy registry include the following:

1) Sufficient information has accumulated to meet the scientific objectives of the registry (i.e., numeric targets or predetermined effect size, such as the "no evidence of risk" or "evidence of relative safety" thresholds defined in the newly created Vaccines and Medications in Pregnancy Surveillance System (VAMPSS):[20] "Estimates of safety cannot be absolute; rather, they reflect the degree of confidence that is consistent with an observation of no increased risk between a given exposure and outcome. As more data are collected over time, power increases; for a null observation, increasing power leads to increasingly narrower confidence bounds and increasing assurance of relative safety.[20]" For example, evidence of relative safety might be reached when the upper bound of the 95% confidence interval excludes a 2 fold increased risk.
2) The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, and/or high rates of loss to followup.
3) Other methods of gathering appropriate information, such as case-control surveillance or large health care databases, become achievable or are deemed preferable.[2]

17.10. Multidrug Pregnancy Registries

A multidrug pregnancy registry actively collects information on exposure to various drug therapies in specific diseases, such as the Anti-retroviral[34] and Antiepileptic drug (NAAED)[33] pregnancy registries. In some cases, a general multidrug registry, such as that conducted by a teratogen information service, collects information on drugs for either unrelated or related indications. Multidrug registries have advantages over single drug registries with respect to both efficiency and economy and allow the examination of polytherapy. They may also have the advantage of having comparison groups of pregnant women unexposed to the specific medical product(s) of interest but with the same indication (e.g. disease registries) or exposed to other drugs for the same indication readily available.

Establishing disease pregnancy registries for common conditions in women of childbearing age (e.g. multiple sclerosis) treated with any available drug would make most sense from a logistic (avoid duplicating efforts), methodological (validity and power) and clinical (comparative safety) point of view.

However, that would require collaboration among companies competing for the same therapeutic area, which may be difficult.

17.11. Multicenter and Global Registries

Like RCTs, registries can be multicenter, national, or international. Currently, registries are centralized by sponsors, CROs, government agencies or academic centers; and typically focus on a single drug, multiple drugs within a class, multiple drugs for different indications, or are disease-based and evaluate drugs used to treat a particular condition.[1] In the future, rather than conducting a new registry for each drug, a global centralized mega pregnancy exposure registry may exist, guided and coordinated by collaborations among regulatory agencies, pharmaceutical companies, contractor organizations and academic centers.[19] Although appealing, in practice, it will be a challenge for this approach to accommodate the case-specific needs for each drug.

The setup, management, and analysis of a locally run registry represent a very different scope than a global registry. The geographic scope includes many challenges (e.g., language, culture, time zone, regulatory differences) that must be taken into consideration in the planning process. A distinct feature of a country-specific registry is that the patient population tends to be more homogeneous with respect to demographic characteristics, exposures, length of followup, and diagnosis of outcomes than international registries.

18. Advantages of Pregnancy Registries

Pregnancy registries are often the initial proactive step in assessing the safety of use during pregnancy of new drugs after they first are marketed because they provide a number of advantages over other approaches:[1] While many pregnant women use medications, their use of individual drugs can be quite rare.[40] By enrolling an exposure group made up only of women who took the medication(s) of interest, pregnancy registries are efficient for evaluating the effects of infrequently used drugs in the population. This is a distinct advantage over other study designs, such as case control studies and small health care utilization databases, which usually do not have sufficient power to evaluate outcomes following rare exposures.

The longitudinal nature of pregnancy registries allows the estimation of absolute risks of pregnancy outcomes. For example, registries that enroll women before any prenatal testing has been performed can estimate the risk of malformations among infants whose mothers used a drug of interest. This is in contrast to case control studies that estimate risk relative to that for a reference group. Information about the absolute risk of outcomes is particularly helpful when counseling women who are planning a pregnancy or already became pregnant while taking a drug. The prospective enrollment facilitates ascertainment of drug exposures close to the time a medication is actually used and before information about the pregnancy outcome is known. When registries interview pregnant women directly, they can obtain accurate information about the timing in relation to gestational age, dose, frequency, and duration of medication use, as well as covariates, and can therefore reduce exposure misclassification, recall bias, and confounding.

Pregnancy registries can compare the risk of outcomes among women who have used a variety of treatments for a single condition, including different monotherapies, different polytherapy combinations, or no treatment at all. This information is useful to both women and health care providers when making decisions about whether to treat a condition during pregnancy and which of multiple alternate therapeutic

strategies to use. An additional advantage is that a single registry can monitor a variety of pregnancy and infant outcomes after medication exposure, including postnatal outcomes.

19. Limitations of Pregnancy Registries

The pregnancy registry approach also has a number of limitations. While they are an efficient means to assess rare exposures, they lack the statistical power to evaluate rare outcomes. Most teratogenic exposures do not increase the prevalence of all malformations, but have a more selective effect on individual defects or distinct patterns of defects. Pregnancy registries are powered to detect common outcomes such as the total prevalence of all malformations, and can detect only very large increases in these rarer individual defects or patterns. However, many drugs associated with adverse effects in pregnancy result in only moderate increases in these rarer outcomes. Therefore, pregnancy registries are limited in their ability to detect teratogenic effects on specific malformations with statistical certainty. As such, registries can generate hypotheses that form the basis of further investigation using complimentary approaches, study designs, and data sources.[20]

Another important limitation of some registries is the lack of a comparable reference group. Ideally, a comparison group should be drawn from the same population as women with the exposure of interest using the same methods for recruitment, enrollment, and ascertainment of outcomes so that both groups have the same baseline risk for adverse pregnancy outcomes. Comparison of registry findings with data from other studies, such as population-based surveillance programs or hospital deliveries, can lead to biased results if the subjects in the reference group have characteristics different from those of the registry participants, or it the methodology for case ascertainment is different. Identifying an appropriate reference group can be particularly difficult for global registries that recruit exposed women from multiple countries with potentially different populations and backgrounds. For registries such as these, a comparable unexposed group may not exist. Even when an internal reference group is recruited, differences between the exposed and unexposed groups in factors such as the indication for the drug or the proportion of subjects that are lost to followup potentially can affect the validity of the results.

An additional consideration is that findings from a pregnancy registry may not be generalizable to the broader population of all women who use a drug. Enrollment of women in pregnancy registries typically is voluntary, self-selected, and registry participants represent a small proportion of all women who have taken a drug. For these reasons, the characteristics and experience of women who participate in a registry may differ from those of nonparticipants, and those characteristics might modify the effect of the drug.

A final limitation of pregnancy registries is the length of time typically required to enroll sufficient numbers of exposed women to generate stable estimates of pregnancy outcomes. This can be affected by the frequency of exposure in the general population, and the methods and extent of recruitment efforts by the registry. Most registries continue for years before publishing final results. This extended period of evaluation before reaching conclusions regarding adverse pregnancy outcomes can be a disadvantage when there are pregnancy outcomes of concern that need to be evaluated quickly or when new therapeutic agents become available.

20. Evaluation of Reports from Pregnancy Registries

It is important to critically assess the results and conclusions of reports from pregnancy registries. Key issues to consider are summarized in Table 27.

Table 27. Issues to Consider when Evaluating Reports from Pregnancy Registries

Area	Issues
Objectives	What question(s) is the registry attempting to answer? Are the design and methods appropriate to do so?
Background	What condition(s) is the drug used to treat (e.g., chronic vs. episodic)? In what settings is the drug likely to be used (e.g., as primary treatment or as adjuvant therapy with other drugs)? What is the recommended therapeutic dose and duration of use? Is the drug likely to be used off-label for conditions other than the stated indication?
Study population	What is the target population from which pregnant women exposed to the drug are drawn? Does the report describe the characteristics of women enrolled in the registry? Could the study subjects differ from women in the target population in ways that would affect the generalizability of the results?
Exposure ascertainment	What are the sources of information about drug exposure (e.g., maternal interviews, physician reports, pharmacy records)? Are these sources likely to provide valid information about how women actually used the drug? Are the exposures ascertained in sufficient detail (e.g., dose, frequency, duration, timing during gestation) to accurately assess the drug's potential effects on the outcome(s) of interests?
Outcome ascertainment	What are the sources of information about pregnancy outcomes, infant and fetal health (e.g., maternal interviews, obstetricians' reports, pediatric records)? Are these sources likely to be knowledgeable about the occurrence of the outcomes being studied? Are outcomes among stillbirths, spontaneous abortions, and elective terminations included? Are the outcomes documented in sufficient detail?
Reference group(s)	What comparison group(s) does the registry utilize? Is an internal comparison group recruited? Are there potential differences between the exposed and comparison groups that could affect the validity of the findings?
Statistical power	Does the sample size provide sufficient statistical power to meet the objective(s)?
Biases	When did subjects enroll (i.e. gestational age at enrollment for exposed and reference groups)? What proportion of registry enrollees did not complete the study (lost to followup)? Do their characteristics differ from those who completed the study in ways that could affect the validity of the results? Are exposed subjects comparable to the reference group? Were the same methods for data collection and outcome definition used in the exposed and reference groups? Are there other possible sources of bias in the results? Are these biases addressed sufficiently in the analyses or sensitivity analyses?
Results	Does the report provide estimates of the absolute risk of the adverse pregnancy outcomes being studied? Are the results generalizable to the broader population of pregnant women who will use the drug?

Area	Issues
Conclusions	Does the report explore possible alternative explanations for the findings? Does the report review and compare findings from other studies that assess the drug's effects during pregnancy, or findings for other drugs used to treat the same condition(s)? Do the registry findings provide information that will be useful to health care providers and women in making clinical decisions about use of the medication and pregnancy management?

21. Summary

Well-designed and executed pregnancy registries are an efficient initial approach to assess the safety of biopharmaceuticals during pregnancy and can provide data that can be used by health care providers for the treatment and counseling of patients who are pregnant or wish to become pregnant. Although pregnancy registries are more appropriate to identify or rule out large increases in the risk for malformations than to identify more modest teratogenic risks, they are a valuable tool to establish safety boundaries around risk estimates as data accumulate. Pregnancy registries have some unique characteristics that make them distinct form other registries or types of surveillance. Critical methodological issues to consider in the design include the prospective enrollment of women before the pregnancy outcome is known, inclusion of a comparable reference group, thoughtful assessment of drug exposure, ascertainment of prenatal and postnatal diagnosis, and validation of outcomes. Chance and potential biases should be considered when interpreting results from any observational study. A surveillance program should consider a combination of different sources of data so that associations detected in one study can be replicated or refuted by others.[20]

References for Chapter 21

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Case Examples for Chapter 21

Case Example 46. Expanding an Ongoing Pregnancy Registry

Description	The Antiretroviral Pregnancy Registry is the oldest ongoing pregnancy exposure registry. This multisponsor, international, voluntary, collaborative registry monitors prenatal exposures to all marketed antiretroviral drugs for potential risk of birth defects.
Sponsor	Abbott Laboratories, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Gilead Sciences Inc, HEC Pharm, Hetero USA, Janssen Infectious Diseases BVBA, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Pfizer Inc, Ranbaxy Inc, Roche, Teva Pharmaceuticals, and ViiV Healthcare (represented by GlaxoSmithKline).
Year Started	1989
Year Ended	Ongoing
No. of Sites	Not site-based; open to all health care providers. Nearly 2,000 health care providers have contributed data to the registry.
No. of Patients	16,732

Challenge

Antiretroviral treatments represent an area of particular concern for monitoring safety in pregnancy. Women may need to take the drugs during pregnancy to manage their own HIV infection and to reduce the risk of transmitting HIV to the infant, but these benefits must be weighed against the risk of teratogenic effects. Because of these factors, it is extremely important for clinicians and patients to understand the risks of using antiretroviral drugs during pregnancy in order to make an informed decision. However, ethical and practical concerns make a randomized trial to gather these data difficult, if not impossible.

In 1989, the first manufacturer of an antiretroviral drug voluntarily initiated a pregnancy exposure registry to track the outcomes of women who had used its product during pregnancy. The purpose of the registry is to collect information on any teratogenic effects of the product by prospectively enrolling women during the course of their pregnancy and following up with them to determine the outcome of the pregnancy. Physicians enroll a patient by providing information on the pregnancy dates, characteristics of the HIV infection, drug dosage, length of therapy, and trimester of exposure to the antiretroviral drug. Information on the pregnancy outcome is gathered through a follow-up form sent to the physician after the expected delivery date.

In 1993, the registry was expanded to include all antiretroviral drugs, as other manufacturers voluntarily joined the registry once their drugs were on the market. The registry is international in scope and allows any health care provider to enroll a patient who has intentional or unintentional use of an antiretroviral drug during pregnancy. The U.S. Food and Drug Administration (FDA), which has used this registry as a

model for new pregnancy registries, now requires participation in the registry for all new and generic antiretroviral drugs.

2012 marks the 20th anniversary of the registry. Since 2006, the registry more than doubled the enrollment of the first 15 years, increasing from 6,893 pregnancies in 2006 to 16,732 in 2012. This increase in enrollment was partly due to the increased number of new antiretroviral medications on the market. In 2006, the registry monitored 28 medications from 8 companies; by 2012, it monitored 36 medications from 18 companies (including manufacturers of both branded and generic products). The registry has also increased enrollment as well as its geographic representation by incorporating the datasets of comparable, completed epidemiologic studies. For example, the registry added data on nearly 1000 women from a study conducted in Brazil and Argentina of ARV-exposed pregnant women who delivered between the years 2002 and 2007.

In addition to this large increase in enrollment, electronic data capture (EDC) was introduced in 2010 as a data collection method for the registry.

In summary, early challenges for the registry included establishing standard processes for monitoring and assessing the safety of drugs during pregnancy. Key challenges in recent years have included managing the methodological and analytic implications of a rapid growth in size and the operational implications of adding EDC.

Proposed Solution

To ensure both rigor and consistency early on, the registry put in place predefined analytic methods and criteria for recognizing a potential teratogenic signal. Tools for coding and classifying birth defects were developed for the registry to maximize the likelihood of identifying a teratogenic signal. This unique system groups birth defects by etiology or embryology rather than by general location or category, as does the Medical Dictionary for Regulatory Activities (MedDRA). Grouping like defects together increases the likelihood of detecting a potential signal. The registry also codes the temporal association between timing of exposure and formation of the birth defect, aiding in signal detection.

Specific monitoring criteria were developed for evaluating signals at various levels, including the Rule of Three (the rule that three exposure-specific cases with the same birth defect require immediate evaluation). This rule is based on the statistical principle that the likelihood of finding at least three of any specific defect in a cohort of 600 or fewer by chance alone is less than 5 percent.

In the last few years of the registry's operation, large increases in enrollment required re-evaluation of the adequacy of existing signal detection rules. The Rule of Three continues to serve an important role; however, understanding weak signals is methodologically challenging. Incorporating enrollments from comparable epidemiologic studies into the registry population has boosted enrollment, increased cultural diversity, and enhanced signal detection capabilities. Each merger of external data prompts the need to re-examine the potential for selection and ascertainment bias.

Operationally, each new participating manufacturer undergoes a series of trainings and is required to obtain IRB approval before participation in the registry. Registry trainings and standard operating procedures are reviewed at biannual steering committee meetings and revised as appropriate.

In expanding the options for data entry into the registry, a hybrid EDC-paper approach was deemed operationally feasible in lieu of an EDC-only approach. This allowed a subset of established reporters to use EDC, while limiting disruption for reporters who preferred to report data on paper CRFs.

Results

The registry now contains data on 16,732 prospective pregnancies with exposure to 36 medications from 18 companies. Approximately 40% of new enrollments in the registry are made using EDC technology.

Registry data have been used in 13 publications, 9 abstracts, and 25 presentations, and the registry design and operation have been the subject of many publications and presentations. The registry findings can help to provide clinicians and patients with information to make informed decisions regarding use of antiretroviral drugs during pregnancy.

Key Point

A pregnancy exposure registry can employ continuous quality improvement practices to identify and define key quality processes and keep the registry current and innovative throughout its life cycle. Having established, standard policies and procedures for coding, monitoring, and analysis was critical in incorporating new partners and data sources quickly and easily. Regular review of these policies and procedures is essential to respond to the changing registry environment.

For More Information

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Case Example 47. Using a Pregnancy Registry to Detect Major Teratogenicity

Description	The International Lamotrigine Pregnancy Registry was established to monitor for the signal of major teratogenicity following in utero exposure to lamotrigine.
Sponsor	GlaxoSmithKline
Year Started	1992
Year Ended	2010
No. of Sites	Not applicable; health care providers reported lamotrigine exposure during pregnancy and subsequent pregnancy outcomes on a voluntary basis.
No. of Patients	1,558

Challenge

Lamotrigine is a second generation anticonvulsant therapy, widely indicated for the treatment of epilepsy. Lamotrigine was approved in the U.S. for the treatment of epilepsy in 1994 and for the treatment of bipolar disorder in 2003. In 1992, following the approvals of lamotrigine in several different European countries, the International Lamotrigine Pregnancy Registry was established to monitor the frequency of major teratogenicity following in utero exposure to lamotrigine. Major congenital malformation (MCMs), identified after birth and before hospital discharge, was the primary outcome evaluated by the registry. The U.S. Centers for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects Program case definition was used to classify MCMs. Due to the rarity of the outcome, the registry needed to enroll enough limotrigine-exposed patients in order to have adequate statistical power to detect changes in MCM frequencies.

Proposed Solution

The registry targeted an enrollment of 1000 limotrigine-exposed pregnant women. Prospective reporting early in pregnancy was encouraged. The registry also received and reviewed retrospective reports, defined as those for which the pregnancy outcome was known at the time of reporting. Due to successful patient enrollment, the registry closed to new prospective enrollments in June 2009, and continued to follow up with existing enrollments through March 2010. The results of the International Lamotrigine Pregnancy Registry were compared descriptively against the results of other ongoing anti-epileptic drug (AED) pregnancy registries. While major teratogenicity was evaluated, the registry was not powered to determine the frequency of specific malformation types; surveillance for specific types using the European Congenital Anomalies and Twins Registers (EUROCAT) network is planned.

Results

At registry closure, over 1500 birth outcomes involving first trimester monotherapy exposure had been evaluated during the 18-year registry period. The registry was thus adequately powered to meet its primary objective, to determine whether the overall rate of major malformations was increased among the offspring of exposed women. The registry did not detect an appreciable increase in the outcome of MCMs overall. Over an 18-year period, 35 infants with MCMs were observed among 1,558 first trimester monotherapy exposures: 2.2% (95% Confidence interval (CI) 1.6%-3.1%). This was similar to estimates

from general population-based cohorts and no pattern of malformation frequency by dose was observed. However, the registry was not powered to exclude increases in the rates of specific defects.

First trimester monotherapy results from the registry were consistent with several other ongoing AED pregnancy registries, such as the North American Anti-epileptic Drug Registry (2.3%, 95% CI 1.3%-3.8%) and the EURAP international pregnancy registry (2.9%, 95% CI 2.1%-4.1%). Monitoring of specific malformations among lamotrigine-exposed pregnancies will continue through case-control surveillance in the EUROCAT network.

Key Point

A drug-specific pregnancy registry can provide valuable information about risks of major congenital malformations following in utero exposure; however, it may take several years to collect enough exposed patients to detect a signal of teratogenicity with sufficient statistical power. For such rare outcomes, accumulating data over long periods of time and from multiple registries is advantageous to monitoring the safety of medical treatments used in pregnancy.

For More Information

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Case Example 48. Implementing a Non-Mandated Pregnancy Registry

Description	The Global Gleevec®/Glivec® & Tasigna® Pregnancy Exposure Registry is an international, prospective, observational registry of women and their offspring exposed to Gleevec®/Glivec® (imatinib) and/or Tasigna® (nilotinib) during pregnancy or within six months prior to pregnancy. The primary objective of the registry is to monitor pregnancies exposed to Gleevec®/Glivec® or Tasigna® (tyrosine kinase inhibitors to treat some cancers) to assess the prevalence of birth defects. Secondary objectives include determining the impact of interrupted treatment on maternal disease status and assessing infant development around 12 months post-delivery.
Sponsor	Novartis
Year Started	2011
Year Ended	Ongoing
No. of Sites	4
No. of Patients	5 (expected enrollment of 150)

Challenge

Chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST) are rare oncologic diseases. Since the approval of Gleevec®/Glivec® in 2001, life expectancy for these diseases has substantially improved and treatment is now considered chronic. Tasigna®, approved for CML treatment in 2007, is shown to have superior efficacy compared to Gleevec®/Glivec®. Patients of child-bearing age

are now contemplating reproductive opportunities that would not have been possible previously, and are requesting information about the safety and effectiveness of these treatments during pregnancy. The sponsor sought to address this unmet medical need by collecting data on pregnancy outcomes and on the disease status of pregnant women who were exposed to Gleevec®/Glivec® or Tasigna® during pregnancy.

Pharmaceutical companies typically establish pregnancy registries when they are mandated to do so by regulatory authorities. This registry is voluntary and was not mandated by regulatory authorities, and consequently the sponsor experienced challenges in study startup and in enrollment. Regulatory requirements in countries outside the US evolved during startup which required revisions to study design. Additionally, both Gleevec®/Glivec® and Tasigna® are classified by the U.S. Food and Drug Administration (FDA) as pregnancy category D, and the prescribing information carries a warning that these drugs should not be administered to pregnant women. Thus, the sponsor was careful to design an awareness campaign that did not promote exposure during pregnancy.

Most existing pregnancy registry models focus primarily on collecting birth outcomes and do not collect maternal disease status or postpartum data. Since this registry was not mandated, and information on maternal health as well as birth outcomes was desired, a novel model was needed.

Proposed Solution

The registry was launched in the U.S. in 2011 and in Russia, the Netherlands and Denmark in 2012. The sponsor adopted a National Coordinator (NC) model for the registry. The NC is a domestic entity that is responsible for submitting the protocol to the appropriate regulatory authority for approval and for facilitating the collection of registry data from multiple sources (e.g., oncologist, hematologist, obstetrician, pediatrician). In the U.S., the NC is a contract research organization; outside the U.S., the NC is a participating physician who has agreed to assume the above responsibilities. Data are collected on maternal disease status at three time points: enrollment, pregnancy outcome, and about 12 months post-delivery according to local standard of care. Data are also collected on the fetus/infant at pregnancy outcome and about 12 months of age.

A website was constructed that provides information about the registry and instructs patients (only in the U.S.) and providers (globally) on how to enroll into the registry. The sponsor worked closely with regulatory authorities to ensure that the information presented on the website is educational and not promotional in nature. Patient recruitment is facilitated through the existing pregnancy reporting infrastructure in the sponsor's safety department; U.S. health care providers calling to report pregnancies are invited to enroll eligible patients into the registry. Additionally, collaborating with patient advocacy groups and preparing durable materials facilitated registry awareness.

Results

The sponsor encountered unanticipated delays and challenges from regulatory authorities, possibly because non-mandated pregnancy registries are unprecedented. Recent EMA legislation expanding the safety reporting requirement for non-interventional studies has necessitated further revisions to the protocol and case report form. Work is continuing on expanding the registry to other countries.

Five patients have been enrolled to date, and this number is expected to increase when the registry's website and awareness materials are approved by the FDA for use in the U.S.

Key Point

Pregnancy registries that are not mandated by regulatory authorities present unique operational challenges. Beginning a study in locations with a favorable regulatory environment may help minimize delays in startup and allow sponsors to apply lessons learned before expanding the registry to other locations. Staying current with regulatory requirements in long-term pregnancy registries is critical to remaining compliant. When collecting data from several different sources (e.g., patients and multiple providers), consider an operational model that centralizes the responsibility for data collection and for Health Authority and Ethics Committee submission and approval.

For More Information

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Case Example 49. Using Proactive Awareness Activities To Recruit Patients for a Pregnancy Exposure Registry

Description	The Ribavirin Pregnancy Registry is a component of the Ribavirin Risk Management Program. It was designed to evaluate the association between ribavirin and birth defects occurring in the offspring of female patients exposed to ribavirin during pregnancy or the 6 months prior to conception, as well as female partners of male patients exposed to ribavirin during the same time period. The registry collects prospective, observational data on pregnancies and outcomes following pregnancy exposure to ribavirin.
Sponsor	Aurobindo Phama USA; Genentech, Inc.; Sandoz Pharmaceuticals Inc.; Schering Corporation, a subsidiary of Merck & Co. Inc.; Teva Pharmaceuticals USA, Inc.; Three Rivers Pharmaceuticals, LLC; Zydus Pharmaceuticals (USA) Inc.
Year Started	2003
Year Ended	Ongoing
No. of Sites	Not applicable (population-based)
No. of Patients	Approximately 230 evaluable pregnancies

Challenge

Ribavirin is used in combination with interferon alfa or pegylated interferon alfa for the treatment of hepatitis C. Chronic hepatitis C presents a serious health concern for approximately three million Americans, as the infection, if left untreated, can lead to end-stage liver disease, primary liver cancer, and death. When used as part of a combination therapy, ribavirin can significantly increase both viral clearance and liver biopsy improvement for hepatitis C patients.

However, ribavirin showed teratogenic properties in all animal models tested, making pregnancy exposure a concern. There are minimal data on ribavirin exposure in human pregnancies. Thus, the U.S. Food and Drug Administration (FDA) designated ribavirin as a Pregnancy Category X product based on the animal data, and ribavirin carries product label warnings against becoming pregnant.

Despite the product warnings, pregnancies continue to occur. Health care professionals have insufficient data on the teratogenic properties of ribavirin in humans to counsel pregnant women exposed to ribavirin either during pregnancy or in the 6 months prior to conception. The registry was established to gather prospective data on ribavirin exposure in pregnancy and pregnancy outcomes to better understand the actual risk.

The registry collects data on direct exposures through the pregnant female and indirect exposures through her male sexual partner. Health care providers, pregnant patients, or pregnant patients' male sexual partners may submit data to the registry. The registry collects minimal, targeted data at each trimester and at the outcome of the pregnancy through the obstetric health care providers. For live births, the registry collects data at 6 months and 12 months after the birth by contacting the pediatric health care provider.

To gather data on these patients, the registry needed to develop proactive awareness activities to make patients and providers aware of the program and encourage enrollment without promoting ribavirin use during pregnancy.

Proposed Solution

The registry team developed a multipronged approach to recruiting patients. First, the team developed a comprehensive Web site with information for patients and providers. The Web site contains fact sheets, data forms, information on how to participate, and contact information. The site also contains a complete slide set that health care providers can use for teaching activities.

While the site contains detailed information on the scientific reasons for the registry, the tone and content of the Web site are patient friendly, making it a good resource for both potential patients and providers.

Next, the team began targeting professional service groups whose members might treat patients with ribavirin exposure during pregnancy. The groups included hepatologists, gastroenterologists, obstetricians, and pediatricians. By contacting the groups' leadership and sending individualized mailings to members, the team hoped to raise awareness across a broad spectrum of providers. The team communicated with nursing groups, including publishing an article in a nursing journal targeted to

gastroenterology nurses, with the goal of utilizing the nurse's role as a patient educator. As a result of these efforts, the American Gastroenterological Association placed a link for the registry Web site on its Web site, and the American Association for the Study of Liver Diseases posted an expert opinion piece written by the former registry advisory board chair on its Web site.

The registry team also raised awareness among professional groups by attending conferences. In 2005, the team presented a poster about the registry, including some information on demographics and program objectives, at the Centers for Disease Control and Prevention (CDC) National Viral Hepatitis Prevention Conference. In 2009, the team presented a poster at the International Society for Pharmacoepidemiology and in 2010 at the conference of the Teratology Society.

To expand awareness efforts to healthcare providers, the registry published results after five years of enrollment in 2010, even though the targeted sample size had not been reached. In 2011, the registry developed an article for PeriFACTS, a continuing education eJournal for OB/GYNs, nurses, and other HCPs, sponsored by the University of Rochester. Beginning in 2012, the registry began providing the executive summary of the annual interim report to health care providers upon request; this summary provides the most up to date snapshot of registry activity.

To raise awareness among patients, the team talked to hepatitis C patient advocacy groups. The registry gained exposure with patients when one patient group wrote an article about the registry for its newsletter and included the registry phone number on its fact sheet. This effort led to many patient-initiated enrollments, despite the lack of patient incentives. In working with patients, the registry has found that emphasizing the goal, which is to gather information to help future patients make better decisions, resonates with patients. Most patients submit data to the registry over the phone, and the rapport that the interviewers have developed with patients has helped to reduce the number of patients who are lost to followup.

In addition to targeting providers and patients directly, the team enlisted the help of public health agencies, since the registry has a strong public health purpose. Registry Web links are posted on the Web sites of the FDA Office of Women's Health and the Department of Veterans Affairs. A description of the registry is posted on ClinicalTrials.gov.

The team also reviewed the registry process to identify any potential barriers to enrollment. Under the initial rules for giving informed consent, the registry call center contacted patients and asked them if they were interested in participating. If patients agreed to participate over the phone, the call center sent a package of information through the mail, including an informed consent document, which the patients needed to sign and return before they could enroll. While many patients agreed to participate over the phone, a much smaller number actually returned the informed consent document. The team identified the process of obtaining written informed consent as a key barrier to enrollment.

After discussions with FDA, the registry team and FDA approached the study institutional review board (IRB) about receiving a waiver of written informed consent because of the public health importance of the registry. The IRB agreed that oral consent over the phone would be sufficient for this study. Now, the call center can complete the enrollment process in a single step, as they can obtain oral consent

over the phone and then proceed with the interview. This change improved and streamlined the enrollment process and significantly increased the number of participants in the registry.

Throughout all of these recruitment activities, the registry team has emphasized that the purpose of the registry is to answer important safety questions for the benefit of future patients and providers. By focusing on the public health purpose of the registry, the team has been able to encourage participation from both patients and providers. The team has also found that a key element of their recruitment strategy is their detailed awareness plan, which calls for completing awareness activities monthly. Because the leadership and membership of professional groups change and new patients begin taking ribavirin, the team has found that continual awareness activities are important for keeping patients and providers aware of the registry.

Results

Through proactive awareness activities, the registry team has generated interest in the project and enrolled approximately 230 exposed pregnancies with outcome information to date. The streamlined oral consent process increased enrollment in this registry.

Key Point

Recruitment activities may include working with professional groups, contacting patient groups, targeting public health agencies, producing publications, and using a Web site to share information. Once recruitment and enrollment have begun, the registry team may need to re-evaluate the process to identify any potential barriers to enrollment if enrollment is not proceeding as planned. If a registry has an ongoing enrollment process, a plan to continually raise awareness about the registry is an important part of the recruitment plan.

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Chapter 22. Quality Improvement Registries

1. Introduction

Quality assessment/ improvement registries (QI registries) seek to use systematic data collection and other tools to improve quality of care. While much of the information contained in the other chapters of this document applies to QI registries, these types of registries face unique challenges in the planning, design, and operation phases. The purpose of this chapter is to describe the unique considerations related to QI registries. Case Examples 50, 51, 52, 53, and 54 offer some descriptions of quality improvement registries.

QI registries may have many purposes, at least one purpose is quality improvement. These registries generally fall into two categories: registries of patients exposed to particular health services (e.g., procedure registry, hospitalization registry) around a relatively short period of time (i.e., an event); and those with a disease/condition tracked over time through multiple provider encounters and/or multiple health services. An important commonality is that one exposure of interest is to health care providers/health care systems. These registries exist at the local, regional, national, and international levels.

QI registries are further distinguished from other types of registries by the tools that are used in conjunction with the systematic collection of data to improve quality at the population and individual patient levels. QI registries leverage the data about the individual patient or population to improve care in a large variety of ways. Examples of tools that facilitate data use for care improvement include patient lists, decision support (typically based on clinical practice guidelines), automated notifications, communications, and patient and population level reporting. For example, a diabetes registry managed by a single institution might provide a listing of all patients in a provider's practice that have diabetes and that are due for a clinical exam or other assessments. Decision support tools exist that assess the structured data on the patient being provided to the registry and display recommendations for care based on evidence-based guidelines. This is a well-reported feature of the American Heart Association's Get With The Guidelines® registries.[1] Certain registry tools will automatically notify a provider if the patient is due for a test, exam, or other milestone. Some tools will even send notifications directly to patients indicating that they are due for an action such as a flu shot. Reports are a key part of quality improvement. These range from reports on individual patients, such as a longitudinal report tracking a key patient outcome, to reports on the population under care by a provider or group of providers either alone or in comparison to others (at the local, regional, or national level). Examples of the latter reports include those that measure process of care (e.g., whether specific care was delivered to appropriate patients at the appropriate time) and those that measure outcomes of care (e.g., average Oswestry score results for patients undergoing particular spine procedures versus similar providers).

QI registries can further support improved quality of care by providing providers and their patients with more detailed information based on the aggregate experience of other patients in the registry. This can include both general information on the natural history of the disease process from the accumulated experience of other patients in the registry as well as more individual-patient level information on specific risk calculators that might help guide treatment decisions. Registries that produce patient-specific predictors of short and long-term outcomes (which can inform patients about themselves) as well as

provider-specific outcomes benchmarked against national data (which can inform patients about the experience and outcomes of their providers) can be the basis of both transparent and shared decisionmaking between patients and their providers.

In addition to these examples are tools that are neither electronic nor necessarily provided through the registry systems. Non-electronic examples range from internal rounds to review registry results and make action plans, to quality-focused national or regional meetings that review treatment gaps identified from the registry data and teach solutions, to printed posters and cards or other reminders that display the key evidence-based recommendations that are measured in the registry. Further, even electronic tools need not be delivered through the registry systems themselves. While in many cases the registries do provide the functionality described above, the same purpose is served when an electronic health record (EHR) provides access to decision support relevant to the goals of the patient registry. In other words, what characterizes QI registries is not the embedding of the tools in the registry but the use of the tools by the providers that participate in the registry to improve the care that they provide and the use of the registry to measure that improvement.

2. Planning

As described in Chapter 2, developing a registry starts with thoughtful planning and goal setting. Planning for a QI registry follows most of the steps outlined in Chapter 2, with some noteworthy differences and additions. A first step in planning is identifying key stakeholders. Similar to other types of registries, regional and national QI registries benefit from broad stakeholder representation, which is necessary but not sufficient for success. In QI registries, the provider needs to be engaged and active as the program is not simply supporting a surveillance function or providing a descriptive or analytic function but often focused on patient and/or provider behavior change. In many QI registries, these active providers are termed 'champions' and are vital for success, particularly early in development.[2] At the local level, the champions are typically the ones asking for the registry and almost by definition are engaged. Selecting stakeholders locally is generally focused on involving those with direct impact on care or those that can support the registry with information, systems, or labor. Yet, the common theme for both local and national QI registries is that the local champions must be successful in actively engaging their colleagues in order for the program to go beyond an 'early adopter' stage and to be sustainable within any local organization. Once a registry matures, other incentives may drive participation (e.g., recognition, competition, financial rewards, regulatory requirements), but the role of the champion in the early phases cannot be overstated.

A second major difference between planning a QI registry and planning other types of registries is the funding model. QI registries use a wide variety of funding models. For example, a regional or national registry may be funded entirely by fees paid by participating providers or hospitals. Alternately, the registry may supplement participation fees with funding from professional associations, specialty societies, industry, foundations, or government agencies. Some QI registries may not charge a participation fee and may receive all of their funding from other organizations. Local QI registries that operate within a single institution may receive all of their funding from the institution or from research grants. The funding model used by a QI registry largely depends on the goals of the registry and the stakeholders in the specific disease area.

Next, in order for a QI registry to meet its goal of improving care, it must provide actionable information for providers and/or participants to be able to modify their behaviors, processes, or systems of care. Actionable information can be provided in the form of patient outcomes measures (e.g., mortality, functional outcomes post discharge) or process of care or quality measures (e.g., compliance with clinical guidelines). While the ultimate goal of a QI registry is to improve patient outcomes by improving quality of care, it is not always possible for a QI registry to focus on patient outcomes measures. In some cases, outcome measures may not exist in the disease area of interest, or the measures may require data collection over a longer period than is feasible in the registry. As a result, QI registries have often focused on process of care or quality measures. While this has been criticized as less important than focusing on measures of patient outcomes, it should be noted that quality measures are generally developed from evidence-based guidelines and emphasize interventions that have been shown to improve long term outcomes, increasingly recognized through standardized processes (e.g., National Quality Forum), and are inherently actionable). Patient outcomes measures, on the other hand, do not yet have consensus across many conditions, are prone to bias in patients lost to followup, and may be expensive and difficult to collect reliably. Furthermore, long-term outcomes are generally not readily available for rapid cycle initiatives and may be too distant temporally from when the care is delivered to support effective behavior change. Despite these challenges, there has been an increasing focus in recent years on including outcome measures instead of or in addition to process of care measures in QI registries. This shift is driven in part by research documenting the lack of correlation between process measures and patient outcomes[3,4,5] and by arguments that health care value is best defined by patient outcomes, not processes of care.[6]

Selecting measures for QI registries typically requires balancing the goals to be relevant and actionable with the desire to meet other needs for providers, such as reporting quality measures to different parties (e.g., accreditation organizations, payers). Frequently, this is further complicated by the lack of harmonization between those measure requirements even in the same patient populations.[7] Even when there is agreement on the type of intervention to be measured and how the intervention is defined, there still may be variability in how the cases that populate the denominator are selected (e.g., by clinical diagnosis, by ICD-9 classification, by CPT codes). In the planning stages of a QI registry, it is useful to consider key parameters for selecting measures. The National Quality Forum offers the following four criteria for measure endorsement, which also apply to measure selection:

1) Important to measure and report to keep our focus on priority areas, where the evidence is highest that measurement can have a positive impact on healthcare quality.
2) Scientifically acceptable, so that the measure when implemented will produce consistent (reliable) and credible (valid) results about the quality of care.
3) Useable and relevant to ensure that intended users — consumers, purchasers, providers, and policymakers — can understand the results of the measure and are likely to find them useful for quality improvement and decisionmaking.
4) Feasible to collect with data that can be readily available for measurement and retrievable without undue burden.[8]

The National Priorities Partnership[9] and the Measure Applications Partnership,[10] both of which grew out of the National Quality Forum and provide support to the U.S. Department of Health and Human Services

on issues related to quality initiatives and performance measurement, also offer useful criteria to consider when selecting measures.

One approach to consider in selecting measures is performing a cross-sectional assessment using the proposed panel of measures to identify the largest gaps between what is recommended in evidence-based guidelines or expected from the literature and what is actually done ('treatment gaps'). The early phase of the registry can then focus on those measures with the most significant gaps and for which there is a clear agreement among practicing physicians that the measure reflects appropriate care. The planning and development process should move from selecting measures to determining which data elements are needed to produce those measures (see Section 4 below). Measures should ideally be introduced with idealized populations of patients in the denominator for whom there is no debate about the appropriateness of the intervention. This may help reduce barriers to implementation that are due to physician resistance based on concerns about appropriateness in individual patients.

Once the measures and related data elements have been selected, pilot testing may be useful to assess the feasibility and burden of participation. Pilot testing may identify issues with the availability of some data elements, inconsistency in definition of data elements across sites, or barriers to participation, such as burden of collecting the data or disagreement about how exclusion criteria are constructed when put into practice. In order for the registry to be successful, participants must find the information provided by the registry useful for measuring and then modifying their behaviors, processes, or systems of care. Pilot testing may enable the registry to improve the content or delivery of reports or other tools prior to the large-scale launch of the program. If pilot testing is included in the plans for a QI registry, the timeline should allow for subsequent revisions to the registry based on the results of the pilot testing.

Change management is also an important consideration in planning a QI registry. QI registries need to be nimble in order to adapt to two continual sources of change. First, new evidence comes forward that changes the way care should be managed, and it is incumbent on the registry owner to make changes so that the registry is both current and relevant. In many registries, such as American Heart Association's Get With The Guidelines® Stroke program and the American Society of Clinical Oncologists' QOPI registry, this process occurs more than once per year. Second, registry participants manage what they measure, and, over time, measures can be rotated in or out of the panel so that attention is focused where it is most critical to overcome a continuing treatment gap or performance deficiency. This requires that the registry have standing governance to make changes over time, a system of data collection and reporting that is flexible enough to rapidly incorporate changes with minimal or no disruption to participants, and sufficient resources to communicate with and train participants on the changes. The governance structure should include individuals who are expert in the area of measurement science as well as in the scientific content. The registry system also needs to continuously respond to additional demands for transmitting quality measures to other parties that may or may not be harmonized (e.g., Physician Quality Reporting System, Meaningful Use reporting, Bridges to Excellence, state department of public health requirements). From a planning standpoint, QI registries should expect ongoing changes to the registry and plan for the resources required to support the changes. While this complicates the use of registry data for research purposes, it is vital that the registry always be perceived first as a tool for improving outcomes. Therefore, whenever changes are made to definitions, elements, or measures, these need to be carefully tracked so that analyses or external reporting of adherence may take these into account if they span time periods in which changes occurred.

3. Legal and Institutional Review Board Issues

As discussed in Chapters 7, 8, and 9, registries navigate a complex sea of legal and regulatory requirements depending on the status of the developer, the purpose of the registry, whether or not identifiable information is collected, the geographic locations in which the data are collected, and the geographic locations in which the data are stored (state laws, international laws, etc.). QI registries face unique challenges in that many institutions' legal departments and Institutional Review Boards (IRBs) may have less familiarity with registries for quality improvement, and, even for experts, the distinction between a quality improvement activity and research may be unclear.[11,12,13,14] Some research has shown that IRBs differ widely in how they differentiate research and quality improvement activities.[15] What is clear is that IRB review and, in particular, informed consent requirements, may not only add burden to the registry but may create biased enrollment that may in turn affect the veracity of the measures being reported.[16] Potential limitations of the IRB process have been identified in other reports, including for comparative effectiveness research, and will not be reviewed here.

For QI registries, which generally fit under the HIPAA health care operations definition, the issues that lead to complexity include whether or not the registry includes research as a primary purpose or any purpose, whether the institutions or practices fall under the Common Rule, and whether informed consent is needed. The Common Rule is discussed in the Chapter 7, and informed consent and quality improvement activities are discussed in Chapter 8. To assist in determining whether a quality improvement activity qualifies as research, the Office for Human Research Protections (OHRP) provides information in the form of a "Frequently Asked Questions" webpage.[17] OHRP notes most quality improvement activities are not considered research and therefore are not subject to the protection of human subjects regulations. However, some quality improvement activities are considered research, and the regulations do apply in those cases. To help determine if a quality improvement activity constitutes research, OHRP suggests addressing the following four questions, in order:

> "(1) does the activity involve *research* (45 CFR 46.102(d));
> (2) does the research activity involve human subjects (45 CFR 46.102(f));
> (3) does the human subjects research qualify for an exemption (45 CFR 46.101(b)); and
> (4) is the non-exempt human subjects research conducted or supported by HHS or otherwise covered by an applicable FWA approved by OHRP."[18]

In addressing these questions, it is important to note the definition of "research" under 45 CFR 46.102(d). "Research" is defined as "…a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge…." OHRP does not view many quality improvement activities as "research" under this definition and provides some examples of the types of activities that are not considered research.[19] It is also important to note the definition of "human subjects" under 45 CFR 46.101(b). "Human subject" is defined as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information." Again, OHRP does not view some quality improvement activities as collecting data on human subjects because data are not identifiable and were not collected through interaction with the individual patient (e.g., abstracted from a medical record).[20]

These questions provide some helpful information in determining whether a quality improvement registry is subject to the protection of human subjects regulations, but some researchers and IRBs have still reported difficulty in this area.[21,22] Remaining questions include, for example, if the registry includes multiple sites, is separate IRB approval from every institution required? If the registry is considered research, in what circumstances is informed consent required?

There have been several recent calls to refine and streamline the IRB process for QI registries,[23] and some of this work is advancing. Recently, OHRP has proposed revisions to the Common Rule that would address some of these issues; the proposed changes were posted for a public comment period, which closed in October 2011.[24] Without some changes and greater clarity around existing regulations as they relate to QI registries, it will be difficult for some registries to be successful.

4. Design

Designing a quality improvement registry presents several challenges, particularly when multiple stakeholders are involved. Staying focused on the registry's key purposes, limiting respondent burden, and being able to make use of all of the data collected are practical considerations in developing programs. First, the type of quality improvement registry needs to be determined. Is the goal to improve the quality of patients with a disease or patients presenting for a singular event in the course of their disease? For example, a QI registry in cardiovascular disease will be different (i.e. sampling, endpoints, measures) if it focuses on patients with coronary artery disease versus if it focuses on patients with a hospitalization for acute coronary syndrome or patients who undergo percutaneous coronary angioplasty as an inpatient or outpatient. In the first example, the registry may need to track patients over time and across different providers; reminder tools may be needed to prompt followup visits or lab tests. In the second example, the registry may need to collect detailed data at a single point in time on a large volume of patients.

Second, QI registries that collect data within a single institution differ from those that collect data at multiple institutions regionally or nationally. Single institution registries, for example, may be designed to fit within specific workflows at the institution or to integrate with one EHR system. They may reflect the specific needs of that institution in terms of addressing treatment gaps, and they may be able to obtain participant buy-in for reporting plans (e.g., for unblinded reporting). Regional or national level registries, on the other hand, must be developed to fit seamlessly into multiple different workflows. These registries must address common treatment gaps that will be relevant to many institutions, and they must develop approaches to reporting that are acceptable to all participants.

The appropriate level of analysis and reporting is an important consideration for designers of QI registries. Reports may provide data at the individual patient, provider, or institution level, or they may provide aggregate data on groups of patients, providers, and institutions. The aggregate groups may be based on similar characteristics (e.g., disease state, hospitals of a similar size), geography, or other factors. The registry may also provide reports to the registry participants, to patients, or to the public. Reports may be unblinded (e.g., the provider is identifiable) or blinded, and they may be provided through the registry or through other means. In designing the registry, consideration should be given to what types of reports will be most relevant for achieving the registry's goals, what types of reports will be acceptable to participants, and how those reports should be presented and delivered. Reporting considerations are discussed further in Section 9 below.

As described above, there are many challenges in selecting existing measures or designing and testing new measures. Once measures have been selected, the 'core data' can be determined. Since QI registries are part of health care operations, it is critical that they do not overly interfere with the efficiency of those operations, and therefore the data collection must be limited to those data elements that are essential for achieving the registry's purpose. One approach to establishing the core data set is to first identify the outcomes or measures of interest and then work backwards to the minimal data set, adding those elements required for risk adjustment or relevant subgroup analyses. For example, the inclusion and exclusion criteria for a measure, as well as information used to group patients into numerator and denominator groups, can be translated into data elements for the registry. Case Example 50 describes this process for the Get With The Guidelines® Stroke program. Depending on the goals of the registry, the core data set may also need to align with data collection requirements for other quality reporting programs.

Many QI registries have gone further by establishing a core data set and an enhanced data set for participating groups that are ready to extend the range of their measurements. This tiered model can be very effective in appealing to a broad range of practices or institutions. Examples include the Get With The Guidelines® program, which allows hospitals to select performance measures or both performance and quality measures, and the American College of Surgeons NSQIP program, which has a core data set and the ability to add targeted procedure modules.

QI registries also may need to develop sampling strategies during the design phase. The goal of sampling in quality improvement registries is to provide representativeness (i.e., reflective of the patients treated by the physician or practice) and precision (i.e., sufficient sample size to provide reasonable intervals around the metrics generated from each practitioner/practice to be useful in before/after or benchmarking comparisons). Sampling frames need to balance simplicity with sustainability. For example, an all comers model is easy to implement but can be difficult to sustain, particularly if the registry utilizes longitudinal followup. For example, an orthopedic registry maintained by a major U.S. center sought to enroll all patients presenting for hip and knee procedures. Since the center performed several thousand procedures each year, within a few short years the numbers of followups being performed climbed to the tens of thousands. This was both expensive and likely unsustainable. On the other hand, a sampling frame can be difficult and confusing. While a sampling frame can be readily administered in a retrospective chart review, it is much more difficult to do so in a prospective registry. Some approaches to this issue have included selecting specific days or weeks in a month for patient enrollment. But, if these frames are known to the practitioners, they can be 'gamed,' and auditing may be necessary to determine if there are sampling inconsistencies. Pilot testing can be useful for assessing the pace of patient enrollment and the feasibility of the sampling frame. Ongoing assessments may also be needed to ensure that the sampling frame is yielding a representative population.

An additional implication when considering how to implement a sampling strategy is that for QI registries in which concurrent case ascertainment and intervention is involved, only those patients that are sampled may benefit from real-time QI intervention and decision-support. In these circumstances, patients who are not sampled are also less likely to receive the best care. This disparity may only increase as EHR-enabled decision support becomes increasingly sophisticated and commonplace.

5. Operational Considerations

As with most registries, the major cost for participants in a QI registry is data collection and entry rather than the cost of the data entry platform or participation fees. Because QI registries are designed to fit within existing health care operations, many of the data elements collected in these registries are already being collected for other purposes (e.g., claims, medical records, other quality reporting programs). QI registries are often managed by clinical staff who are less familiar with clinical research and who must fit registry data collection into their daily routines. Both of these factors make integration with existing health information technology systems or other data collection programs attractive options for some QI registries. Integration may take many forms. For example, data from billing systems may be extracted to assist with identifying patients or to pull in basic information on the patients. EHRs may contain a large amount of the data needed for the registry, and integration with the EHR system could substantially reduce the data collection burden on sites. However, integration with EHRs can be complex, particularly for registries at the regional or national level that need to extract data from multiple systems. A critical challenge is that the attribution of clinical diagnoses in the context of routine patient care is often not consistent with the strict coding criteria for registries, making integration with EHR systems more complex. Chapter 15 discusses integration of registries with EHR systems. Another alternative for some disease areas is to integrate data collection for the registry with data collection for other quality initiatives (e.g., Joint Commission, CMS). Typically, these types of integration can only provide some of the necessary data; participants must collect and enter additional data to complete the CRFs.

The burden of data collection is an important factor in participant recruitment and retention. Much of the recruitment and retention discussion in Chapter 10 applies to QI registries. However, one area in which QI registries differ from other types of registries is in the motivations for participation. Sites may participate in other registries because of interest in the research question or as part of mandated participation for state or federal payment or regulatory requirements. When participation is for research purposes, they may hope to connect with other providers treating similar patients or contribute to knowledge in this area. In contrast to registries designed for other purposes, participants in QI registries expect to use the registry data and tools to effect change within their organization. Participation in a QI registry and related improvement activities can require significant time and resources, and incentives for participation must be tailored to the needs of the participants. For example, recognition programs, support for QI activities, QI tools, and benchmarking reports may all be attractive incentives for participants. In addition, tiered programs, as noted above, can be an effective approach to encouraging participation from a wide variety of practice or institution types. Understanding the clinical background of the stakeholders (e.g., nurses, physicians, allied health, and quality improvement professionals) and their interest in the program is critical to designing appropriate incentives for participation.

6. Quality Improvement Tools

As described above, QI tools are a unique and central component of QI registries. QI tools generally leverage the data in the registry to provide information to participants with the goal of improving quality of care. Examples of QI tools that draw on registry data include patient lists, automated notifications and other types of communications, decision support tools, and reports. Generally, QI tools are designed to meet one of two goals: care delivery and coordination or population measurement. Care delivery and coordination tools aim to improve care at the individual patient level. For example, an automated notification may inform a provider that a specific patient is due for an exam. Population measurement

tools track activity at the population level, with the goal of assessing overall quality improvement and identifying areas for future improvement activities. For example, a report may be used to track an institution's performance on key measures over time and compared to other similar institutions. These types of reports can be used to demonstrate both initial and sustained improvements. Table 28 below summarizes some common types of QI tools in these two categories and describes their uses.

QI registries may incorporate various tools, depending on the needs of their participants and the goals of the registry. Table 29 below describes the types of functionalities that have been implemented in three different registries – two at the national level and one at the regional level.

Table 28. Common Quality Improvement Tools

Major Goal	QI Tool	Description
Care delivery and coordination	Patient lists	Lists of patients with a particular condition who may be due for an exam, procedure, etc.
	Patient level reports	Summarize data on an individual patient (e.g., longitudinal data on blood pressure readings).
	Automated notifications	Prompt provider or patient when an exam or other action is needed.
	Automated communications	Summarize patient information in a format that can be shared with the patient or other providers.
	Decision support tools	Provide recommendations for care for an individual patient using evidence-based guidelines.
Population measurement	Population level standardized reports	Provide an analysis of population-level compliance with QI measures or other summaries (e.g., patient outcomes across the population).
	Benchmarking reports	Compare population-level data for various types of providers.
	Ad-hoc reports	Enable participants to analyze registry data to explore their own questions and to support continuous quality improvement activities
	Population level dashboards	Provide snapshot look at QI progress and areas for continued improvement.
	3rd party quality reporting	Enables registry data to be leveraged for reporting to 3rd party quality reporting initiatives.

Table 29. Quality Improvement Tools Implemented in Three Registries

Registry	Disease/Condition	Functionalities Implemented
AHA Get With The Guidelines®	Heart failure Stroke	• Decision support (guidelines) • Communication tools • Patient education materials • Real-time quality reports with benchmarks • Transmission to 3rd parties
MaineHealth Clinical Improvement Registry	Diabetes	• Patient care 'gap' reports • Decision support • Transmission to 3rd parties
National Comprehensive Cancer Network (NCCN)	Cancer	• Patient care 'gap' reports • Center level reports • Education materials

7. Quality Assurance

In addition to developing data elements and QI tools, QI registries must pay careful attention to quality assurance issues. Quality assurance, which is covered in Chapter 11.3, is important for any registry to ensure that appropriate patients are being enrolled and the data being collected are accurate. Data quality issues in registries may result from inadequate training, incomplete case identification or sampling, misunderstanding or misapplication of inclusion/exclusion criteria, or misinterpretation of data elements. Quality assurance activities can help to identify these types of issues and improve the overall quality of the registry data. QI registries can use quality assurance activities to address these common issues, but they must also be alert to data quality issues that are unique to QI registries. Unlike other registries, many QI registries are linked to economic incentives, such as licensure or access to patients, incentive payments, or recognition or certification. These are strong motivators for participation in the registry, but they may also lead to issues with data quality. In particular, 'cherry picking,' which refers to the non-random selection of patients so that those patients with the best outcomes are enrolled in the registry, is a concern for QI registries. Whenever data are being abstracted from source documents by hand and then entered manually into electronic data entry systems, there is a risk of typographical errors, errors in unit conversions (e.g., 12 hour to military time, milligrams to grams). Automated systems for error checking can reduce the risk of errors being entered into the registry when range checks and valid data formats are built into the data capture platform.

Auditing is one approach to quality assurance for QI registries. Auditing may involve on-site audits, in which a trained individual reviews registry data against source documents, or remote audits, in which the source documents are sent to a central location for review against the registry data. Because auditing all sites and all patients is cost-prohibitive, registries may audit a percentage of sites and/or a percentage of patients. QI registries should determine if they will audit data, and, if so, how they will conduct the audits. A risk-based approach may be useful for developing an auditing plan. In a risk-based approach, the registry assesses the risk for intentional error in data entry or patient selection. Registries that may have an increased risk of intentional error are mandatory registries, registries with public reporting, or registries that are linked to economic incentives. Registries with an increased risk may decide to pursue more rigorous auditing programs than registries with a lower risk. For example, a voluntary registry with confidential reporting may elect to do a remote audit of a small percentage of sites and patients each year. A registry with public reporting that is linked to patient access, on the other hand, may audit a larger number of sites and patients each year, with a particular focus on key outcomes that are included in the publically reported measures.

Questions to consider when developing a quality assurance plan involving auditing include: what percentage of sites should be audited each year; what percentage of data should be audited (all data elements for a sample of patients or only key data elements for performance measures); how sites should be selected for auditing (random, targeted, etc.); on-site audits vs. remote audits; and what constitutes passing an audit. Depending on the purpose of the registry, quality assurance plans may also address issues with missing data (e.g., what percentage of missing data is expected? Are data missing at random?) or patients who are lost to followup (e.g., what lost to followup rate is anticipated? Are certain subgroups of patients more likely to be lost to followup?). Lastly, quality assurance plans must consider how to address data quality issues. Audits and other quality assurance activities may identify problem areas in the registry data set. In some cases, such as when the problem is isolated to one or two sites, additional training may resolve the issue. In other cases, such as when the issue is occurring at multiple

sites, data elements, documentation, or study procedures may need to be modified. In rare instances, quality assurance activities may identify significant performance issues at an individual site. The issues could be intentional (e.g., cherry picking) or unintentional (e.g., data entry errors). The registry should have a plan in place for addressing these types of issues.

8. Analytical Considerations

While registries are powerful tools for understanding and improving quality of care, several analytical issues need to be considered. In general, the observational design of registries requires careful consideration of potential sources of bias and confounding that exist due to the non-randomization of treatments or other sources. These sources of bias and confounding can threaten the validity of findings. Fortunately, the problems associated with observational study designs are well known, and a number of analytical strategies are available for producing robust analyses. Despite the many tools to handle analytical problems, limitations due to observational design, structure of data, measured and unmeasured confounding, and missing data should be readily acknowledged. Below is a brief description of several considerations when analyzing QI registry data and how investigators commonly address the problems.

Observational designs used in registries offer the ability to study large cohorts of patients, allowing for careful description of patterns of care or variations in practice compared to what is considered appropriate or best care. While not an explicit intention, registries are often used to evaluate an effect of a treatment or intervention. The lack of randomization in registries, which limits causal inferences, is an important consideration. For example, in a randomized trial, a treatment or intervention can be evaluated for efficacy because different treatment options have an equal chance of being assigned. Another important characteristic that observational studies may lack is the chance of actually receiving a treatment. In a randomized trial, subjects meet a set if inclusion criteria and therefore have an equal chance of receiving a given treatment. However, in a registry, there are likely patients that have no chance of receiving a treatment. As a result, some inferences cannot be generalized across all patients in the registry.

An inherent but commonly ignored issue is the structure of health or registry data. Namely, physicians manage patients with routine processes, and physicians practice within hospitals or other settings that also share directly or indirectly common approaches. These clusters or "hierarchical" relationships within the data may influence results if ignored. For example, for a given hospital, a type of procedure may be preferred due to similar training experiences from surgeons. Common processes or patient selections are also more likely within a hospital than compared to another hospital. These observations form a cluster and cannot be assumed to be independent. Without accounting for the clustering of care, incorrect conclusions could be made. Models that deal with these types of clustered data, often referred to as hierarchical models, can address this problem. These models may also be described as multi-level, mixed, or random effects models. The exact approach depends on the main goal of an analysis, but typically includes fixed effects, which have limited number of possible values, and random effects, which represent a sample of elements drawn from a larger population of effects. Thus, a multilevel analysis allows incorporation of variables measured at different levels of the hierarchy and accounts for the attribute that outcomes of different patients under the care of a single physician or within the same hospital are correlated.

Adequate sample size for research questions is also an important consideration. In general, registries allow large cohorts of patients to be enrolled, but, depending on the question, sample sizes may be highly

restricted (e.g., in the case of extremely rare exposures or outcomes). For example, a comparative effectiveness research question may address anticoagulation in patients with atrial fibrillation. As the analysis population is defined based on eligibility criteria, including whether patients are naïve to the therapy of interest, sample sizes with the exposure may become extremely small. Likewise, an outcome of angioedema may be extremely rare, and, if being evaluated with a new therapeutic, both the exposure and outcome may be too small of sample to fully evaluate. Thus, careful attention to the likely exposure population after establishing eligibility criteria as well as the likely number of events or outcomes of interest is extremely important. In cases where sample sizes become small, it is important to determine whether adequate power exists to reject the null hypothesis.

Confounding is a frequent challenge for observational studies, and a variety of analytical techniques can be employed to account for this problem. When a characteristic correlates with both the exposure of interest and the outcome of interest, it is important to account for the relationship. For example, age is often related to mortality and may also be related to use of a given process. In a sufficiently large clinical trial, age generally is balanced between those with and without the exposure or intervention. However, in an observational study, the confounding factor of age needs to be addressed through risk adjustment. Most studies will use regression models to account for observed confounders and adjust for outcome comparisons. Others may use matching or stratification techniques to adjust for the imbalance in important characteristics associated with the outcome. Finally, another approach being used more frequently is the use of propensity scores that take a set of confounders and reduce them into a single balancing score that can be used to compare outcomes within different groups.

As QI registries have evolved, an important attribute is defining eligibility for a process measure. The denominator for patients eligible for a process measure should be carefully defined based on clinical criteria, with those with a contraindication for a process excluded. The definition of eligibility in a process measure is critical for accurate profiling of hospitals and health care providers. Without such careful, clear definitions, it would be challenging to benchmark sites by performance.

With any registry or research study, data completeness needs to be considered when assessing the quality of the study. Reasons for missing data vary depending on the study or data collection efforts. For many registries, data completeness depends on what is routinely available in the medical record. Missing data may be considered ignorable if the characteristics associated with the missingness are already observable and therefore included in analysis. Other missing data may not ignorable either because of its importance or because the missingness cannot be explained by other characteristics. In these cases, methods for addressing the missingness need to be considered. Various options for handling the degree of missing data including discarding data, using data conveniently available, or imputing data with either simple methods (i.e., mean) or through multiple imputation methods.

9. Reporting to Providers and the Public

An important component of quality improvement registries is the reporting of information to participants, and, in some cases, to the public. The relatively recent origin of clinical data registries was directly related to early public reporting initiatives by the federal government. Shortly after the 1986 publication of unadjusted mortality rates by the Health Care Financing Administration, the predecessor of CMS, a number of states (e.g., the New York Cardiac Surgery Reporting System),[25,26] regions (e.g., Northern New England Cardiovascular Disease Study Group, or NNE),[27,28] government agencies (e.g., the

Veteran's Administration),[29,30,31] and professional organizations (e.g., Society of Thoracic Surgeons)[32,33,34] developed clinical data registries. Many of these focused on cardiac surgery. Its index procedure, coronary artery bypass grafting (CABG) is the most frequently performed of all major operations, it is expensive, and it has well-defined adverse endpoints.

Registry developers recognized that the HCFA initiative had ushered in a new era of healthcare transparency and accountability. However, its methodology did not accurately characterize provider performance because it used claims data and failed to adjust for preoperative patient severity.[35] Clinical registries, and the risk-adjusted analyses derived from them, were designed to address these deficiencies. States such as New York, Pennsylvania, New Jersey, California, and Massachusetts developed public report cards for consumers, while professional organizations and regional collaborations used registry data to confidentially feedback results to providers and to develop evidence-based best practice initiatives.[36,37]

The impact of public reporting on healthcare quality remains uncertain. One randomized trial demonstrated that heart attack survival improved with public reporting,[38] and there is evidence that low-performing hospitals are more likely to initiate quality improvement initiatives in a public reporting environment.[39] However, a comprehensive review[40] found generally weak evidence for the association between public reporting and quality improvement, with the possible exception of cardiac surgery, where results improved significantly after the initial publication of report cards in New York two decades ago.[41,42,43] Some studies have questioned whether this improvement was the direct result of public reporting, as contiguous areas without public reporting also experienced declining mortality rates.[44] Similar improvements have been achieved with completely confidential feedback or regional collaboration in northern New England[45] and in Ontario.[46] Thus, there appear to be many effective ways to improve healthcare quality—public reporting, confidential provider feedback, professional collaborations, state regulatory oversight—but the common denominator among them is a formal system for collecting and analyzing accurate, credible data,[47] such as registries.

Public reporting should theoretically affect consumer choice of providers and redirect market share to higher performers. However, empirical data failed to demonstrate this following the HCFA hospital mortality rate publications,[48] and CABG report cards had no substantial effect on referral patterns or market share of high and low performing hospitals in New York[49,50] or Pennsylvania.[51,52] Studies suggest numerous explanations for these findings, including lack of consumer awareness of and access to report cards; the multiplicity of report cards; difficulty in interpreting performance reports; credibility concerns; small differences among providers; lack of "newsworthiness"; the difficulty of using report cards for urgent or emergent situations; and the finite ability of highly ranked providers to accept increased demand.[53,54,55] Professor Judith Hibbard and colleagues have suggested report card formats that enhance the ability of consumers to accurately interpret accurate report cards, including visual aids (e.g., star ratings) that synthesize complex information into easily understandable signals.[56,57] A recent Kaiser Family Foundation survey[58] suggests that, particularly among more educated patients, the use of objective ratings to choose providers has steadily increased over the past decade, and health reform is likely to accelerate this trend.

The potential benefits of public reporting must be weighed against the unintended negative consequences, such as "gaming" of the reporting system.[59,60] The most concerning negative consequence is risk aversion, the reluctance of physicians and surgeons to accept high-risk patients because of their anticipated negative effect on their report card ratings. Because these highest risk patients may derive the greatest benefit from aggressive intervention, risk aversion may produce a net decrement in public health and a net increase in long-term costs because the best treatments were not initially used.[61,62,63] Risk aversion unquestionably exists, but its extent and overall population impact are difficult to quantify. CABG risk aversion may have occurred in New York[64,65] and Pennsylvania,[66] but studies in California[67] and England[68] have not demonstrated similar findings. Numerous studies document probable risk aversion in percutaneous coronary interventions.[69,70,71] Possible approaches to mitigate risk aversion include demonstrating to providers the adequacy of risk-adjustment and modifying those models when appropriate; excluding highest risk patients from reporting; separate reporting of highest risk patients; and careful clinical review of patients turned down for interventions.

Irrespective of its end results, many believe that public reporting is a fundamental ethical obligation of physicians.[72,73] It addresses the patient right of autonomy or self-determination in decisionmaking. Whether or not they choose to exercise this right, patients making a choice about treatments should be fully informed, which arguably includes their right to know the comparative performance of potential providers.

When a decision has been made to publicly report outcomes, such measures must meet strict criteria. Professional organizations have emphasized the need to use high quality, audited clinical data whenever possible, and to employ the most appropriate statistical methodologies.[74,75] Professional society guidelines provide recommendations of varying strength and evidence strength, whereas performance measures should be a select subset of these guidelines that have the highest level of evidence and strongest class of recommendation (e.g., ACC/AHA class 1[recommended] or 3 [not indicated, or harmful], level A evidence). National Quality Forum requirements for performance measure endorsement have recently been updated. In addition to the four basic requirements of Importance, Scientific Acceptability, Usability, and Feasibility, they emphasize the need for robust, systematic evaluation of the evidence base and comprehensive testing of reliability and validity.[76,77,78]

The unit of analysis in public reporting may be controversial. Many states report results for some procedures at the physician or surgeon level, but in many healthcare areas sample sizes and the small amount of variation attributable to the physician make it difficult to reliably discriminate performance.[79,80,81] Compiling data from a variety of process and outcome endpoints may help to mitigate sample size issues, as may aggregation of results over multiple years.

Report cards at the individual physician level may be more likely to cause risk aversion compared with group or hospital-level reports. Changes in health care delivery models must also be considered. As patient care is increasingly provided by teams of providers that may even cross traditional specialty boundaries, individual physician reporting may become less relevant and feasible. Reimbursement will increasingly be based on the overall care provided to a patient or population, and leaders will have a direct financial incentive to assess the performance of individual physicians in such care groups (e.g., ACOs), whether or not such results are publicly reported.

10. Use of QI Registry Data for Research Studies

An emerging trend is the use of data from QI registries to support additional studies. QI registries may collect large volumes of clinical data that can be used to support research studies. Studies using data from QI registries generally occur in one of two ways. First, the registry may be modified to collect additional data for a substudy. For example, a registry may collect in-hospital data on patients admitted to the hospital for a specific procedure. To study long-term outcomes of the procedure, the registry protocol may be modified to collect followup data for a subset of patients. An example of this approach was the OPTIMIZE-HF registry, which collected in-hospital data on patients admitted with heart failure. A subset of patients provided consent to be contacted after six months to collect additional data.[3] QI registries can also be modified to support other types of studies, such as studies where a subset of participating sites are randomized (cluster randomization) or a subset of patients are randomized (experimental trial). When modifying the registry protocol to support a substudy, the impact on the primary purpose of the registry must be considered, as well as any additional ethical or regulatory requirements introduced by the new data collection effort.

A second approach to using QI registries to support additional studies is to use the registry data, either alone or linked to another dataset. For example, a registry that collects in-hospital data may be linked to a claims database to obtain information on long-term outcomes or to examine other questions.[82] In these cases, the technical, legal, and ethical considerations related to linking registry datasets discussed in Chapter 16. Regardless of which approach is used, researchers using data from a QI registry for additional research studies must understand how the data are collected and how patients are enrolled in the primary registry in order to draw appropriate conclusions from the new study.

11. Limitations of Current QI Registries

To summarize some of the key points above, the ideal QI registry collects uniform data on risk factors, treatments, and outcomes at key points for a particular disease or treatment. It obtains the data from multiple sources, across care settings and leverages existing health information technology (HIT) systems through interoperability and other data sets (from registries, claims, national indices, etc.) through linkage. Such a registry uses standardized methods to assure that the patients sampled are representative, that data are of high quality and that it is comparable across providers. Such registries provide feedback at the patient and population level, and, in addition to facilitating quality improvement, they perform quality reporting to third parties. Importantly, they maintain high levels of participation by providers and patients and have a long term, sustainable business model.

Clearly, most QI registries do not achieve the ideal. The term 'QI registries' is currently used to refer to a broad spectrum of registries, from local or regional registries aimed at improving care for a specific patient population to large, national registries with sophisticated benchmarking data. Many current QI registries focus on isolated conditions or procedures (e.g., the ACC NCDR Cath/PCI Registry; the STS Adult Cardiac Surgery Database). Health reform will require the acquisition of data about the overall, comprehensive care of conditions such as coronary artery disease, or of populations.[83] This may be facilitated by linkages among related data registries, which might include outpatient preventative care, inpatient acute care and procedures, rehabilitation, and chronic disease management.

Current QI registries also have temporal limitations. They characteristically collect data only in-hospital or for 30 days after admission or a procedure. However, patients, payers, and regulators are also

interested in longer-term, longitudinal outcomes such as survival, readmission, reintervention, and cumulative resource use. Such information is useful for shared decisionmaking and for comparative effectiveness research. By linking together robust clinical data registries and administrative databases such as MEDPAR or the Social Security Death Master File[84,85] that provide long-term data, many of these current limitations of clinical registries would be mitigated.

In order for such linkages to be implemented, a number of challenges would need to be overcome. These include a lack of standardized data sets; difficulties collecting data across care settings; inability to leverage existing HIT systems to reduce duplication of clinician effort; inability to link to other data sources that might reduce data collection burden or enrich outcomes; significant variation in the quality of methods used to collect and report data; and quite different levels of participation and business models. Even registries in related conditions may not be fully compatible.

Potential solutions to such issues have been identified.[86] These include, for example, condition and cross-condition efforts to standardize common or core data element specifications, data quality and audit standards, and methodological considerations such as risk-adjustment. Collecting data across care settings will be improved by solving the patient identity management issues (discussed in Chapter 17), which will require clarification and perhaps revision of HIPAA and Common Rule regulations. Overcoming interoperability issues through the promulgation of open standards (e.g., HITSP TP-50) as described in Chapter 15 could have dramatic impact if adopted widely by EHR systems and registries.

Significant hospital data collection costs are additional limitations of clinical registries. Some data elements such as lab values may be automatically extracted from EHRs, but detailed clinical data may still require manual extraction. Existing national registries must develop sustainable business models, and there must be incentives and assistance for the development of new registries where none currently exist.

12. Summary

QI registries have documented success at improving quality of care at the local, regional, and national levels. While QI registries differ in their area of focus, choice of measures, and level of reporting, their consistent features are the use of systematic data collection and other tools to improve quality of care. QI registries also differ from other types of registries in many ways, such as in their use of provider "champions," the inclusion of actionable measures, the frequency of major changes to the registry data collection, the motivations for participation, and the use of blinded or unblinded quality reports to providers, and, in some cases, the public. Because of these differences, QI registries face special challenges, particularly in the planning, design, and operations phases. This chapter describes those challenges and discusses best practices, where appropriate.

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Case Examples for Chapter 22

Case Example 50. Using Recognition Measures To Develop a Dataset

Description	Get With The Guidelines® is the flagship program for in-hospital quality improvement of the American Heart Association (AHA) and American Stroke Association (ASA). The Get With The Guidelines® Stroke program supports point of care data collection and real time reports that are aligned with the latest evidence-based guidelines. The reports include Achievement, Quality, Reporting and Descriptive measures that allow hospitals to trend their performance related to clinical and process outcomes.
Sponsor	American Heart Association/American Stroke Association
Year Started	2003
Year Ended	Ongoing
No. of Sites	1,664
No. of Patients	2,063,439

Challenge

The primary purpose of the program is to improve the quality of in-hospital care for stroke patients. The program uses the PDSA (plan, do, study, act) quality improvement cycle, in which hospitals plan quality improvement initiatives, implement them, study the results, and then make adjustments to the initiatives. To help hospitals implement this cycle, the program uses a registry to collect data on stroke patients and generate real-time reports showing compliance with a set of standardized stroke recognition and quality measures. The reports also include benchmarking capabilities, enabling hospitals to compare themselves with other hospitals at a national and regional level, as well as with similar hospitals based on size or type of institution.

In developing the registry, the team faced the challenge of creating a dataset that would be comprehensive enough to satisfy evidence-based medicine but manageable by hospitals participating in the program. The program does not provide reimbursements to hospitals entering data, so it needed to keep the dataset as small as possible while still maintaining the ability to measure quality improvement.

Proposed Solution

The team began developing the dataset by working backward from the recognition measures. Recognition measures, based on the sponsor's guidelines for stroke care, contain detailed inclusion and exclusion criteria to determine the measure population, and they group patients into denominator and numerator groups. Using these criteria, the team developed a dataset that asked the questions necessary to determine compliance with each of the guidelines. The team then added additional questions to gather information on the patient population characteristics. Since the inception of the program, additional data elements and measure reports have been added or updated to maintain alignment with the current stroke guidelines. Over time, certain measures have also been promoted or

demoted from the higher tiers of recognition measures depending on current science and changes in quality improvement focus.

Results

By using this approach, the registry team was able to create the necessary dataset for measuring compliance with stroke guidelines. The program was launched in 2003 and now has 1,664 hospitals and 2,063,439 stroke patient records. The data from the program have been used in several abstracts and have resulted in 38 manuscripts since 2007.

Key Point

Registry teams should focus on the outcomes or endpoints of interest when selecting data elements. In cases where compliance with guidelines or quality measures is the outcome of interest, teams can work backward from the guidelines or measures to develop the minimum necessary dataset for their registry.

For More Information

http://www.heart.org.

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Case Example 51. Managing Care and Quality Improvement for Chronic Diseases

Description	The Tri State Child Health Services Web-based asthma registry is part of an asthma improvement collaborative aimed at improving evidence-based care and outcomes while strengthening improvement capacity of primary care practices.
Sponsor	Physician-Hospital Organization (PHO) affiliated with Cincinnati Children's Hospital Medical Center
Year Started	2003
Year Ended	Ongoing
No. of Sites	39 community-based pediatric practices
No. of Patients	12,365 children with asthma

Challenge

Asthma, a highly prevalent chronic disease managed in the primary care setting, has proven to be amenable to quality improvement initiatives. This collaborative effort between the PHO and Cincinnati Children's Hospital Medical Center was initiated in 2003 with goals of improving evidence-based care, reducing adverse outcomes, such as asthma-related emergency room visits and missed schooldays, and strengthening the quality of knowledge and capacity within primary care practices. As the asthma initiative spans 39 primary care practices and encompasses approximately 35 percent of the region's pediatric asthma population, the PHO needed to implement strategies for improving network-level, population-based process and outcome measures.

Proposed Solution

To address the project's focus on improving process and outcome measures across a large network, the asthma collaborative decided to implement a centralized, Web-based asthma registry. Key measures of effective control and management of asthma (based on the National Heart, Lung, and Blood Institute's guidelines) are captured via a self-reported clinical assessment form and decision support tool completed by parents and physicians at the point of care. The questions address missed schooldays and workdays, parent's confidence in managing asthma, health resource utilization (e.g., emergency room visits), parent and physician rating of disease control, and other topics. In addition, the clinical assessment form facilitates interactive dialogue between the physician and family during office visits.

The Web-based registry allows real-time reporting at the patient, practice, and network level. Reporting is transparent, with comparative practice data that support the identification of best practices and shared learning. In addition, reporting functionalities support tracking of longitudinal data and the identification of high-risk patients. The Web-based registry also provides access to real-time utilization reports with emergency room visit and admission dates. All reports are available to participating practices and physicians at any time.

Results

The registry provides essential data for identifying best practices and tracking improvement. The network has documented improvement against standard process and outcome measures.

Key Point

Registries can be useful tools for quality improvement initiatives in chronic disease areas. By collecting standardized data and sharing the data in patient-, practice-, and network-level reports, registries can track adherence to guidelines and evidence-based practices, and provide information to support ongoing quality improvement.

For More Information

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Case Example 52. Use of Reporting Tools to Promote Quality Improvement

Description	The Quality Oncology Practice Initiative (QOPI®) is a quality assessment and improvement program for oncology practices.
Sponsor	American Society of Clinical Oncology (ASCO)
Year Started	Pilot program started in 2002 and registry was launched to full ASCO membership in 2006.
Year Ended	Ongoing
No. of Sites	801 registered practices
No. of Patients	Approximately 50,000 patient charts per year

Challenge

The 1999 Institute of Medicine report "Ensuring Quality Cancer Care" identified the opportunity for quality improvement initiatives in oncology. By starting with individual practices, a clear path to nationwide impact was identified. The report set forth recommendations including to "measure and monitor the quality of care using a core set of quality measures." In order to promote this endeavor, a methodology and registry were needed.

Proposed Solution

In 2002, ASCO, in conjunction with a community of oncologists, developed QOPI®, a voluntary pilot program to allow participants to assess and improve cancer care within their own practices. The oncologist-led program created quality measures, developed methodology for data collection and analysis, and tested the feasibility of the pilot program prior to offering access to the registry to all Society membership in 2006. The registry provides comparison data to practices on over 100 quality metrics that practices and practitioners can use to compare their performance to that of their peers, at both the practice and practitioner level. A team of oncologists, researchers, and staff select, adapt, and develop metrics based on clinical guidelines and expert consensus opinion. Practices and institutions register and manually submit abstracted patient chart data through a web-based interface during twice-per-year data collection periods. Once the data collection periods close, the data are analyzed and practices can view reports showing their performance and scores based on quality measures for that round.

Results

Approximately 600 practices representing nearly 15% of US practitioners have now contributed data to the registry. Changes in performance rates have been compared among metrics surrounding the domains of core, end-of-life, symptom management, breast cancer, colorectal cancer, and Non-Hodgkin lymphoma. For example, in a 2010 analysis of registry data, practices completing multiple data collection cycles with the registry had better performance on care of pain for end-of-life care (63%) when compared to practices participating in the registry for the first time (47%). Registry participants who participated in multiple data collection cycles also demonstrated better performance in the rate of documenting discussions of hospice and palliative care, and higher rates of hospice enrollment, when compared to participants who participated in just a single cycle.

Key Point

Access to performance reports can inform physician behavior or be used to demonstrate the need for process improvements within a practice. A registry can provide a systematic approach to data collection to support the ongoing use of self-assessment and benchmark performance reports to facilitate quality improvement.

For More Information

http://qopi.asco.org/

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Case Example 53. Using Registries to Drive Quality Improvement in Chronic Conditions

Description	The National Parkinson Foundation Quality Improvement Initiative (NPF-QII) is a registry-based quality care program that captures longitudinal data on clinical interventions and patient-reported outcomes to identify, implement, and disseminate best practices for the treatment and management of Parkinson's disease.
Sponsor	National Parkinson Foundation
Year Started	2009
Year Ended	Ongoing
No. of Sites	20 centers across U.S., Canada, and internationally
No. of Patients	5,000 patients as of May 2012; 20,000 targeted enrollment

Challenge

Parkinson's disease (PD), an incurable, progressive neurogenerative disorder associated with a high burden of disease, presents unique challenges for quality improvement initiatives. Treatments for PD generally focus on reducing patients' symptoms and improving quality of life. Unlike other chronic conditions where improvement can be measured in terms of well-defined outcomes such as survival or

cardiovascular events, quality improvement in PD can best be measured using patient-based outcomes. However, identifying appropriate patient-based outcomes for this disease can be a challenge. In addition, variability exists in the clinical diagnosis, management, and treatment of PD. Studies have shown that PD patients treated by a neurologist experience better outcomes, such as a decrease in hip fractures or nursing home placement. However, the specific management and treatment strategies used by these specialists have not been studied or well-described. The lack of evidence-based treatment standards warranted a data-driven approach to identify and understand best practices that improve the quality of care and quality of life for PD patients.

Proposed Solution

In 2009, the National Parkinson Foundation (NPF) launched an initiative to improve the quality of care in PD. To support an evidence-based approach, the foundation initiated a PD registry to capture clinical interventions and patient-reported outcomes over time from multiple centers across the U.S., Canada and internationally. The initiative, led by a steering committee of movement disorders neurologists, is a unique effort in PD research because of its ability to collect long-term, longitudinal data from multiple centers and its focus on patient-based outcomes data, rather than process of care measures. The aims of the registry are to accelerate clinical discovery, promote collaborative science, and drive advancements in clinical practice toward patient-centered care.

Results

As of May 2012, the registry includes over 5,000 patients from 20 centers; second and third year data are available for 3,000 and 500 patients, respectively. Patients' encounter-based data, including demographics, comorbidities, hospitalizations, falls, medications, treatments, and outcomes, are collected annually on brief data collection forms. The registry database includes a diverse population of PD patients, and analyses have confirmed variation in practice patterns across centers. Important findings have resulted from the registry data, including understanding factors and predictors of patients' quality of life and caregiver burden. Additional cross-sectional and longitudinal analyses on physician care and patient outcome data are planned to describe practice patterns across the registry, identify and improve understanding of best practices, and support the development of guidelines.

Many neurologists were initially doubtful about the value of a registry in this disease area. For the most part, their past experience was with mortality-based registries based around interventions or fatal illnesses; these failed to model a disease with complex, heterogeneous symptomology where the pathology could not be directly measured. Increasingly, providers have recognized the value of the statistical power and nuanced insight that can be leveraged in this large and detailed registry of expert care.

Key Point

Registry-based quality improvement programs can be useful in many clinical settings, from in-hospital care (e.g., heart failure) to chronic progressive diseases (e.g., PD). The design of the registry and the quality improvement initiative must reflect the nature of the disease and the state of existing evidence. For chronic, progressive diseases, registries can be a useful tool for identifying, developing, and disseminating guidelines for best practices to improve quality of care.

For More Information
http://www.parkinson.org/Improving-Care/Research/Quality-Improvement-Initiative

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Case Example 54. Clarifying the Federal Regulatory Requirements for Quality Improvement Registries

Description	The National Neurosurgery Quality and Outcomes Database (N^2QOD) is a prospective, longitudinal registry designed to measure and improve neurosurgical and spine surgical care as it exists in the real-world health care setting.
Sponsor	American Association of Neurological Surgeons (AANS)
Year Started	2011
Year Ended	Ongoing
No. of Sites	30 US neuropractice groups expected in the first year
No. of Patients	7,000 patients expected in the first year

Challenge

N^2QOD was formed with the aim of measuring the quality of real-world neurosurgical and spine surgery care, and the registry defined that "quality" as safety and effectiveness. Given this definition, a patient outcome-centered approach to data collection was necessary. This patient-centeredness is aligned with the priorities of groups such as the Patient-Centered Outcomes Research Institute and the Agency for Healthcare Research and Quality and reflects a wider trend in quality improvement (QI) science moving away from processes and process-based measures to patient outcomes and outcome measures.

This move towards patient outcomes necessitates a shift in the way QI registries interact with patients. It also presents challenges for institutional review boards (IRBs) reviewing these projects. IRBs can determine that these projects are either "healthcare operations" or "human subjects research", as defined by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Common Rule. If an IRB determines that a registry constitutes "healthcare operations" (i.e., data collection used for issues such as clinical care, administrative use, or quality assessment), then neither IRB approval nor informed consent is required. If an IRB determines that a registry constitutes "human subjects research," the registry falls under IRB purview, and the IRB may determine that informed consent is required of registry participants, or it may grant a waiver of informed consent.

Whether an IRB determines a registry to be "healthcare operations" or "human subjects research" can have profound operational and analytic impacts on the registry. In particular, QI registries designated by

an IRB as research and required to collect informed consent from participants can experience a reduction in enrollment numbers and risk introducing selection bias into the registry population.

The registry was introduced to neurosurgical practice sites in January 2011, and was initially reviewed by 11 IRBs over a four month period. Six of those evaluations resulted in classifications of the registry as quality improvement (QI). The remaining five IRBs classified the same project description as human subjects research, and insisted on full IRB oversight and the requirement for informed consent.

Proposed Solution

Given this mixed interpretation of federal regulations from local IRBs, the AANS approached the Department of Health and Human Services' (DHHS) Office of Human Research Protections (OHRP) in May 2011 to request a formal review of the registry. AANS and OHRP engaged in regular communication over the course of several months, and convened a multistakeholder meeting at the White House which included representatives from OHRP, the Office of the President, Centers for Medicare and Medicaid Services, Food and Drug Administration, Department of Veterans Affairs, DHHS Office of Civil Rights, and three clinical specialty societies, including neurosurgery.

Results

In August 2011, OHRP clarified that, based on these communications and an examination of the registry, the sites participating in N^2QOD were not engaged in human subjects research, and therefore the regulations requiring IRB oversight did not apply. This communication from OHRP is now provided to sites enrolling in N^2QOD to support their IRB review process.

At the time of this writing, the registry has been formally reviewed (or re-reviewed) by 28 IRBs. To date, 27 of the IRBs have classified it as healthcare operations and have waived the requirement for IRB review. The remaining IRB has classified the same project description as research, and has issued a waiver of consent for the project. Approximately 30 additional sites are still in various stages of institutional review. In summary, the OHRP opinion strongly influenced local IRB analyses of the registry.

In July 2011, OHRP released an Advanced Notice of Proposed Rulemaking (ANPRM) for Revisions to the Common Rule. These revisions are intended to improve human subject research while also reducing burdens, delays, and ambiguity for investigators and research subjects.

Key Point

QI registries that are focused on patient outcomes should be aware of the complexities around varied interpretation by multiple IRBs and should plan sufficient time and resources to address these complexities.

For More Information

http://www.neuropoint.org

Department of Health and Human Services. Office of Human Research Protections. "ANPRM for Revision to Common Rule." Available at: http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html. Last accessed on 20 June 2012.

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Chapter 23. Registries for Medical Devices

1. Introduction

Medical device registries are critical for the identification and study of medical devices outcomes. Device registries are used for many purposes, including short- and long-term surveillance, fulfillment of postmarket observational study commitments for regulatory bodies, and comparative safety and effectiveness assessments, including those in under-studied subpopulations (see Chapter 1 for extensive discussion on the definition and purposes of registries in general). Medical device registries play an increasingly important role in bridging the gap between device performance in clinical trials and their use in routine practice over time. Unlike clinical trials, device registries allow assessment of medical device performance in a real world setting. Registries contain data on large numbers of patients receiving care in diverse clinical settings and include clinical outcomes over time, thus providing a critical platform for capturing the experience with a medical device throughout the device and patient lifecycle. Moreover, by linking device exposures and long-term outcomes, registries permit followup that can span decades.

While devices share some similarities with drugs, several major issues unique to devices require special consideration in order to construct and use a medical device registry successfully. Outcomes associated with medical devices can be affected not only by underlying patient factors and device factors (such as biomaterials), but also by user interface (e.g., surgical technique or surgical preference and experience) and ancillary technologies (e.g., choice of imaging). Adverse effects of devices can be localized (e.g., stent thrombosis), but may be more systemic (e.g., toxic, allergic, autoimmune effects). Furthermore, additional hazards may be related to human factor errors such as poor design or adverse interactions (e.g., drug-device or electromagnetic interference). Finally, reasons for device malfunctions may be very diverse, ranging from manufacturing problems and design-induced errors to environmental factors (e.g., humidity) and poor maintenance. Also, although certain malfunctions or device performance issues may appear to be similar, their root cause may vary.

Special challenges related to registry design, data collection, and analysis include the need for unique identification of devices, including device modifications and device components; information on user interface (e.g., surgical technique); ancillary technology and therapies (e.g., drug exposures); detection of device performance issues; the need for followup; and healthcare provider experience and learning.

This chapter will address two topics related to medical device registries: challenges in design and data collection and potential uses of emerging technology. The chapter begins with a discussion of the major considerations that influence the design of device registries and the data that must be collected. Potential approaches to address a variety of design challenges are described. The chapter then discusses emerging technologies that will potentially allow integration of automated device data capture into registry datasets. Case Examples 55, 56, 57, and 58 offer some descriptions of medical device registries.

2. Different Lifecycles between Drugs and Devices

Regulatory oversight of the approximately 1,700 marketed device types in the U.S. is achieved through the use of regulatory controls and the classification process to assure reasonable device safety and effectiveness. The U.S. Food and Drug Administration (FDA) classes I, II, and III are based on the level of control necessary to assure the safety and effectiveness of the device, which includes the intended use

and indications for use of the device. General controls, such as product registration with the FDA, good manufacturing techniques, proper branding and labeling, and notification of the FDA before marketing, and general reporting procedures, are sufficient for class I devices, which are those of lowest risk. General and special controls, such as device-tracking, mandatory performance standards, and post-market surveillance, are required for class II devices. All other devices fall into class III devices (highest risk), most of which require clinical data in support of premarket applications. In addition, the current paradigm encouraged by the Total Product Life Cycle (TPLC)[1] model aims to apply knowledge acquired during product development to future generations of products. This useful framework establishes a solid baseline for understanding effectiveness and safety in devices, but much more information is necessary to fully understand these products during the lifecycle of innovation.

Differences between drugs and devices persist throughout TPLC. Drug modifications occur slowly if at all, whereas device technologies often experience rapid and continuous changes over time, potentially driven by user feedback and involving the use of new materials and approaches.[2,3] Device registries must capture experiences with modifications of an individual and/or class of devices over time. In addition, device performance is affected by factors beyond the device itself, such as operator skill and experience. Sedrakyan and colleagues provide a comprehensive summary of the critical components of device evaluation, with a specific focus on implantable medical devices (IMD).[4] The observational data builds on randomized controlled trial (RCT) data to include both on and off-label use of the IMD and highlights the impact that insurance, distance to qualified providers, and geographic location have on both device use and outcomes.

3. Design and Data Collection Considerations

As with all registries, the primary purpose of a medical device registry will guide design options. Many factors related to registry design are similar to those discussed in Chapter 3, such as selection of a study design and sample size considerations. However, some distinctive features of a medical device registry require additional planning. It is critical that the registry is adaptable to various needs that arise during the lifecycle of device innovation. Some challenges include lack of unique device identifiers, including model/version control and component identification; adequately capturing device malfunctions and failures; the need for longer followup; and impact of provider experience, training, and choice of device. It is informative that some device registries have been developed from procedure registries, with the addition of device identification modules. In these cases, likely risks of device failures may be identified prior to consequential clinical signs and symptoms, allowing for device fixes before harms are experienced by the patient. This chapter will provide general suggestions for addressing these challenges, and although each device registry is unique and will require a solution appropriate for its specific purpose, general principles apply in many cases.

3.1. Device Identification

Currently, although Unique Device Identifiers (UDI) are available for some medical devices (in the form of GTIN or HIBC identifiers), they are not routinely captured in observational data sources like billing claims data or registries, as is the case with National Drug Codes which permit universal drug identification. The inability to identify specific devices affects registry design and data collection and poses challenges for researchers and regulators. Compounding the problem is the fact that device modifications are frequent and part of the business model for manufacturing and innovation. Researchers may connect safety and effectiveness to a class/subset of devices, rather than to the device generally.

Hence, it is critically important to identify an individual device accurately. Related challenges include the lack of standardized definitions and attribute (descriptor) creation based on specific device product codes; difficulties in data collection, such as transmitting information from electronic medical records (EMR) to registries or automated data capture such as those related to barcode scanning accuracy;[5] and hurdles in maintaining master product lists.

Based on a Congressional mandate (Section 226 of the FDA Amendments Act of 2007 and Section 614 of the FDA Safety and Innovations Act), FDA recently issued a draft rule detailing the requirements of manufacturers to have UDIs for their products, and to have this requirement phased in over several years. This FDA initiative eventually will assist with many of the challenges posed by the current lack of standard identifiers for medical devices. In the meantime, several approaches may be used to capture identity in the absence of a UDI that is unique across all devices. For example, some devices have identifiers, such as catalogue, model, serial, and lot numbers, that are unique to a particular manufacturer's device. While these are not standardized and there may be several components from different manufacturers with similar catalogue or model numbers, these numbers can facilitate device identification and tracking when combined.

Thus, prior to full UDI adoption and implementation, researchers must be creative in collecting device information and taking advantage of UDI-like data to fill the gap created by the lack of identifiers. For example, the Society of Thoracic Surgeons Adult Cardiac Database developed a data collection form with an exhaustive list of various heart valve devices. This checklist enables registry participants to collect any information that could be relevant to their practice. Orthopedic registries worldwide are taking advantage of catalogue numbers and lot or serial numbers in order to classify and uniquely identify products. An inefficient but at times appropriate solution is to include device photos in the registry. This strategy is most applicable in settings with few devices on the market that have marked differences in design that can be captured with photographs.

3.2. Device Performance

There are numerous types of performance issues with devices, making it difficult to capture all potential performance issues, failure modes and adverse events in a single device registry. The performance issues may be related to software, hardware, biomaterials, sterility, or other issues. Additionally, similar performance problems (e.g., pacemaker oversensing) could have various root causes and some may or may not manifest clinically (e.g., breast implant rupture). Importantly, although clinical trials may provide some knowledge of failure rates and timing, the propensity to develop these failures is limited during the registry design phase. While the discussion of adverse event reporting requirements for device registries is outside the scope of this chapter, careful consideration of anticipated categories of performance issues is important in registry design. Researchers should consider methods of adjudication and verification of issues with device performance during the design phase in order to ensure collection of all data elements needed to inform those discussions. It is also important to consider how potential performance issues will be detected for the particular device.

Automated surveillance within the registry is an advanced approach to identifying select performance issues within a device (those that manifest uniquely and clinically). When implemented correctly, it can permit real-time evaluation of performance issues within a large sample/population. Surveillance, however, is a complex endeavor, and standardized data elements and collection procedures are required,

likely across multiple institutions or registries. There are several examples of successful registry implementations for surveillance in cardiovascular disease. The Data Extraction and Longitudinal Trend Analysis (DELTA) network study was the first computerized safety surveillance proof-of-concept study for cardiovascular medical devices. This multicenter prospective observational study was designed for safety evaluation of drug eluting coronary stents, embolic protection devices, and vascular closure devices used during percutaneous coronary intervention.[6] It used standard data elements from the American College of Cardiology National Cardiovascular Data Registry (NCDR), which facilitated aggregation of safety events across institutions.

3.3. Device Systems and Components

In many cases, the device of interest for a registry is either part of a larger system of devices or contains multiple components that are considered devices themselves. Issues around the lack of unique identifiers persist and are accompanied by the additional challenge of determining which component is responsible for the performance issues. Sometimes, device components are cleared or approved separately by the FDA. When a registry is designed to understand effectiveness and safety and the device of interest is dependent on accompanying devices included in the same system, information on all components must be captured in enough detail to assess how well the device of interest is functioning. If an adverse event occurs, regulators must be able to pinpoint which component of the system of devices requires action.

In some instances, devices are approved by the FDA as full systems rather than singular components. Examples of this include implantable pacemaker and implantable cardioverter defibrillator systems that involve implantable leads, pulse generators, and external programmers, and angioplasty and stenting systems that involve balloon catheters or stents coupled with guide-wires. In these cases, surgeons may 'mix and match' multiple manufactures or multiple brands into one system. Such mixing presents a data collection issue as well as an analytical challenge. Heterogeneous devices may need to be grouped together in order to perform analysis, and assumptions about homogeneity may not hold. Components of the newly created system may have different stages of expiration, or timelines for useful life, which could alter the effectiveness or long-term safety of the overall system. Because of the varying lifecycles or expiration terms for components in the same system, components may be replaced at different rates. Registries can address this by collecting data on the system as a whole and then attempting to obtain the useful lifetime for each component. Eventually, UDIs will capture expiration dates and registries may no longer need to do this.

In addition to the actual device, some implantable devices require assistance from procedural devices, including other commodity devices or operative instruments, or ancillary devices, such as imaging. In these cases, additional information must be collected. For example, in hernia repair, information on the method of mesh adhesion, such as staples, glue, or sutures, may be necessary for collection, as these adhesives could interact with a specific type of mesh and affect device performance. Researchers should consider the role of these factors and how they can be captured in the data collection process.

3.4. Drug / Device Combinations

Device/drug combinations have become increasingly common over the past decade. Because the development processes for drugs and devices differ, combination products face different challenges. For example, drug-eluting stents (DES) are an example of a product where the device, a bare-metal stent, has been enhanced by the addition of an immunosuppressant or mitotic inhibitor[7] and its elution polymer

coating. In 2003, the FDA approved the addition of drug to stents for a subset of cardiac patients with uncomplicated coronary lesions.[8] In these patients, there was a decrease in coronary restenosis causing repeat revascularization 9 months after stent implantation compared with bare-metal stents. However, as the adoption rate of DES increased, the population of patients in which they were implanted changed – they tended be sicker patients. Moreover, stent thrombosis, a rare but serious adverse event, was higher in DES patients at one-year compared to bare metal stent patients.[9,10,11] Stent thrombosis represented a localized device failure mode with serious and unique clinical manifestations. In cases like this, registries are a critical tool for understanding the long-term safety and effectiveness of the technology.[12,13,14] Special considerations in registry design include separate collection of concomitant drug dosing information and attention to the medications that the patient is taking during implantation in order to flag possible drug interactions. It is also important to prospectively collect concurrent medications that the patient is using over time, again in order to understand potential interactions.

3.5. Obtaining Sufficient Follow-up Information

Obtaining sufficient followup, and as complete case ascertainment as possible, is an issue for all studies, and many of these challenges are addressed in Chapters 3 and 10. However, long-term followup is a particular concern with implantable devices, as well as other products such as ablation and radiation therapy devices. Clinical trials have relatively short followup for implantable devices that are expected to stay in the body indefinitely or until replaced with similar device. These devices are typically studied for less than 5 years pre-market, but are intended to work for decades. While followup time in the initial period of implantation is useful, an indefinite followup registry imbedded within a clinical practice has the ability to answer questions concerning device safety and effectiveness over the full product lifecycle. Few registries have sufficient followup for endpoints of device performance, continuous effectiveness, and safety. One of the best examples is the National Joint Replacement Registry of Australia,[15] which has followup of greater than 10 years.

A unique challenge for device registries is that once a device is implanted, a patient does not have to return to the doctor if they do not have any issues, as opposed to a therapeutic situation where patients return for prescription refills. As a result, collecting followup data both directly from patients and through the healthcare provider is a useful tool for patient retention. Loss to followup differentially for patients that do not experience complications is a risk and underscores the importance of achieving reasonably complete followup on all patients through well-designed continuity of care delivery settings.[16] Long- term data on medical devices can also be obtained through linking registries with administrative billing data or other clinically rich data sources, although limitations such as lack of test results or reasons for procedures may exist.

3.6. Provider Experience and Training

Provider experience and training can influence the selection of device, device performance, and patient outcomes, particularly for implantable devices. Surgeons generally have a preference in terms of selection of devices, and although sometimes this is based on clinical appropriateness, it can also be based on marketing or familiarity with a particular brand. Group purchasing organizations, cost, provider contracts, reimbursement, and other market forces may also influence selection and, in some of these cases, surgeons may not have a choice of device. Additionally, provider experience and surgical/procedural skill can greatly influence effectiveness and safety of devices.[17]

Because of the impact that the healthcare provider can have on device performance, collection of a provider identifier, identifiable or synthetic, may be an important component of a registry. The collection of identifiable provider codes raise concerns about data security and may present a deterrent for physician participation. Novel methods of using synthetic identifiers, such as those that integrate provider characteristics, may need to be considered.

Device-specific training is an important element of a medical device registry that is not an issue in a drug registry. Device premarket studies are typically smaller than drugs studies. Post-approval, regulatory agencies are concerned about training program quality. Often, an observational study is required to formally evaluate the appropriateness of physician training. Regardless of whether regulators have mandated this type of study, the integration of training information into data collection is recommended by regulators. The importance of this varies based on device type. For example, in the case of the introduction of a new carotid stent, experience with similar stent types, such as balloon-expandable or self-expanding, can be translated to observed patient outcomes. However, if a percutaneous valve is being studied, specific training on the delivery technique required by that specific valve is important. The amount of training required to ensure safe application of technology is often unclear.9

Beyond training, there are experience-oriented factors that should be considered in analyses and training evaluation: practitioner training; practitioner annual volume; practitioner lifetime volume; facility volume; and facility characteristics such as academic teaching status. It is important to distinguish between these factors because there is a threshold effect for each. Some factors, particularly lifetime volume, have not been well documented or analyzed. For this reason, registries should consider capturing this data despite the challenges. For others, such as hospital volume and academic teaching status, the relationships with complications, revision surgery, length of hospital stay, and mortality are well documented.[18, 19, 20] It is ideal to have training and volume information in the registry, but this may not always be realistic. If this is deemed critical, information needs to be collected on provider experience and training at registry initiation and supplemented if any training programs occur during the registry development.

Registry design teams should consider how provider training and learning curves could be handled during analysis. Particularly for devices with few qualified surgeons, clustering may be an issue in analysis. Sample size may need to increase, and statistical methods that account for clustering such as generalized estimating equations should be utilized. Adjustment by surgical volume, either on the hospital or provider level, might also be appropriate.[21] For example, some studies have shown that categories integrating both of these components as one adjustment variable (e.g., high volume hospital and surgeon; high volume hospital with low volume surgeon; low volume hospital with high volume surgeon; both low volume) are useful.[22]

3.7. Summary of Design and Data Collection Considerations

Although device registries are similar to other registries operationally, the challenges outlined above are critical to consider during the registry design phase. Careful review of the unique features of medical device registries can result in high quality, useful studies of device performance. Medical devices must be identified accurately and their attributes classified according to standard nomenclature. Minimum recommended identity variables include manufacturer, product name, lot number (where applicable), catalog number, serial number (where applicable and with appropriate consideration for protected health

information), description of device, and device attributes. These implant characteristics can then be linked to patient, surgeon, hospital, and procedural data along with outcomes of interest. For these reasons, diligence in information security is warranted when identity variables are being collected, and these data should not be included in limited datasets. (See Chapter 7 for a full discussion of the implications of collecting individually identifiable data within a patient registry.) Device identification and attribute classification require constant maintenance as new devices are introduced into the market. In the future, UDIs will significantly facilitate this process. A standard minimum dataset targeted toward device registries would be useful for supporting strong registry designs and to facilitate linkages with other data sources.

The definition and validity of device performance issues is another important element. In developing a device registry, the modes of failures and definitions must be clearly defined. Performance issues should be adjudicated and verified for accuracy. It is also crucial to track all device components. Device systems such as leads and generators in implantable cardioverter defibrillators (ICDs) must both be tracked in case either component fails. Collecting information to track drug/device interactions is also critical. Finally, sufficient followup of patients must be established for registries to provide longitudinal outcomes.

4. Regulatory Uses and Considerations

The FDA has for a long time been actively engaged in the use and development of registries for both pre- and postmarket assessments of device safety and effectiveness. For premarket considerations, device registries have: 1) provided data to support development, design, and use of comparators (both concurrent and historical) in clinical trials (e.g., INTERMACS, heart valves); 2) provided access to products (outside of IDE trials) (e.g., PFO occluders); 3) enhanced safety assessments via broader analysis of adverse events (e.g., adhesion barriers); and 4) expedited approval of device modifications or labeling (e.g., intraocular lenses). Postmarket applications of device registries have included frequent use in FDA mandated studies (e.g., drug-eluting coronary stents), use in enhanced passive surveillance efforts (e.g., INTERMACS, CART-CL), use in exploratory efforts to expand FDA Sentinel capabilities, both in active surveillance and data source linkage (e.g., DELTA), and use in discretionary applied research as noted below.

Over time, various stakeholder communities have increased their efforts to foster the development of clinical registries as a valuable postmarket tool for capturing utilization of devices, identifying early signals, and studying postmarket performance of medical technology. Some of these efforts transformed what were primarily procedure registries into procedure/device registries for certain targeted devices of interest. Examples of long-standing collaborative efforts include those between FDA and professional society databases such as the American College of Cardiology NCDR.[23] This collaboration resulted in one of the largest observational studies on hemostasis devices using NCDR registry data.[24] In addition, the FDA collaborated with Duke University and the Society of Thoracic Surgeons to study the outcomes of transmyocardial revascularization procedures using the Adult Cardiac Surgery Database.[25] More recently, the national multi-stakeholder community, including professional societies, the FDA, and the Centers for Medicare and Medicaid Services worked together to establish the first national transcatheter valve therapy (TVT) registry to capture transcathether aortic valve replacement therapies.[26] This effort aims to foster both pre- and postmarket uses for future TVT devices and indications. In the orthopedic

arena, the FDA led the development of International Consortium of Orthopedic Registries to advance the methodological infrastructure for studying performance and clinical outcomes of orthopedic implants.[27]

The FDA continues to foster the development of registries in key product areas. It also recognizes the need for a national perspective on device registry development that considers how best to: 1) leverage existing experience and expertise; 2) establish common data elements across registries; 3) share evolving methodological tools; 4) enhance interoperability between standard electronic health records and registries; 5) create sustainable business models; and 6) adopt robust and transparent governance practices.

5. Potential Uses of Emerging Technology

Registries may soon be able to take advantage of emerging technology for data transmission. New technologies can enable medical devices to transmit data directly to electronic medical records and other patient management systems. Ultimately, this type of data may be sent directly to a patient registry, reducing the burden of data entry and increasing the timeliness of registry data.

These new technologies are currently at various stages of development. Automatic measurement and adjustment of programming to provide optimal settings is a potential area of innovation that would provide efficiencies in the use of pacemakers and other implantable devices. Feasibility for this has been demonstrated by the Automaticity registry, which aims to evaluate physician's acceptance of automatic algorithms for ventricular capture, automatic sensing, and automatic optimization of sensor settings.[28,29] The Automaticity team concluded that project team followup and avoidance of reprogramming due to the automated programming can increase effective use of hospital time and resources. This would be a useful technology for registries because all automated changes can be collected at one followup time point, rather than collecting each change ad-hoc as it occurs.

Diagnostics for implantable devices are another area of technical improvement. Implantable devices, such as ICDs, pacemakers, and cardiac resynchronization therapy devices, can track heart rate, heart rate variability, respiration rate, atrial tachyarrhythmia and ventricular tachyarrhythmia recurrence and duration, intrathoracic impedance, symptom markers, and patient activity.[30] This diagnostic information can be provided directly to EMRs and feed into registries, in many cases continuously. Although the clinical application of this capability is still being examined, the benefits in efficient, timely data capture are clear.

The fascinating pace of emerging medical technologies and information science applications are expected to further shape the healthcare research. Further development and integration of device-based registries into national postmarket infrastructure creates opportunities for novel methodology developments, harmonization, sharing, and combining of data.

6. Summary

Medical device registries can be designed for a variety of purposes. They can provide useful information on long-term effectiveness and safety of drugs, as well as the impact of factors such as surgical technique, surgeon, hospital, and patient characteristics. Like all studies, medical device registries have some limitations. Failure to control for often-complex confounding variables and the inability to take into account device version changes, surgical technique, and other unique factors can lead to false or misleading conclusions. In addition, medical device registries are limited in their ability to identify small

differences in performance among relatively similar, well-designed devices.[31] However, careful consideration of the unique nature of medical devices in registry design and analysis will allow medical device registries to bridge the gap between device performance in clinical trials and use in routine practice over time.

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Case Examples for Chapter 23

Case Example 55. Designing a Registry To Study the Effectiveness of a Device Training Program for Providers

Description	The Carotid Artery Stenting with Emboli Protection Surveillance Post-Marketing Study (CASES-PMS) was designed to assess the outcomes of carotid artery stent procedures for the treatment of obstructive artery disease during real-world use. The primary purpose of the registry was to evaluate outcomes in the periapproval setting, including the use of a detailed training program for physicians not experienced in carotid artery stenting.
Sponsor	Cordis Corporation
Year Started	2004
Year Ended	2006
No. of Sites	74
No. of Patients	1,493

Challenge

In 2004, the sponsor received approval for a carotid stent procedure from the U.S. Food and Drug Administration (FDA), largely because of the results of the Stenting and Angioplasty With Protection in Patients at HIgh Risk for Endarterectomy (SAPPHIRE) clinical trial. The SAPPHIRE trial studied the results of stent procedures performed by experts in the field. While the trial provided strong data to support the approval of the carotid stent, FDA and the Centers for Medicare & Medicaid Services (CMS) both questioned whether the outcomes of the trial were generalizable to procedures performed by physicians without prior experience in carotid artery stenting.

To respond to the FDA and CMS requests, the sponsor needed to design a study to confirm the safety and effectiveness of carotid artery stenting in a variety of settings. The study needed to gather data from academic and nonacademic settings, from physicians with various levels of carotid stenting experience, from settings with varying levels of carotid stenting volume, and from a geographically diverse mix of sites. The study would also need to examine the effectiveness of a training program that the sponsor had designed to teach physicians about the stenting procedure.

Proposed Solution

The sponsor designed a comprehensive training program for physicians and other health care professionals. The training program, which began in 2004, included didactic review, case observations and simulation training, and hands-on experience. To study the effectiveness of the training program and to provide data on the clinical safety and effectiveness of carotid stenting in a variety of settings, the sponsor designed and launched the registry in 2004.

The registry was a multicenter, prospective, observational study designed to assess stenting outcomes in relation to the outcomes of the SAPPHIRE trial (historic comparison group). The study enrolled 1,493

patients from 74 sites, using inclusion and exclusion criteria that matched those of the SAPPHIRE trial. The patients in the study were high-surgical-risk patients with de novo atherosclerotic or postendarterectomy restenotic obstructive lesions in native carotid arteries. Study participants completed clinical followups at 30 days and again at 1 year after the procedure. The 30-day assessments included a neurological examination by an independent neurologist and an evaluation of adverse events. The study defined the 30-day major adverse event rate as the 30-day composite of all deaths, myocardial infarctions, and strokes.

Results

The 30-day major adverse event rate of 5.0 percent met the criteria for noninferiority to the outcomes of stented patients from the pivotal SAPPHIRE trial. Outcomes were similar across levels of physician experience, carotid stent volume, geographic location, and presence/absence of the training program. The initial findings show that a comprehensive, formal training program in carotid stenting enables physicians from multiple specialties with varying levels of experience in carotid stenting to achieve outcomes similar to those achieved by the experts in the clinical trial.

Key Point

An observational registry can provide the necessary data for a postmarket evaluation of devices that are dependent on newly acquired skills. The registry can provide data to assess both the clinical safety of the device and the effectiveness and success of a training program.

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Case Example 56. Identifying and Responding to Adverse Events Found in a Registry Database

Description	The Kaiser Permanente National Total Joint Replacement Registry (TJRR) was developed by orthopedic surgeons to improve patient safety and quality and to support research activities. The TJRR tracks all Kaiser Foundation Health Plan members undergoing elective primary and revision total knee and hip replacement. The purposes of the registry are to (1) monitor revision, failure, and rates of key complications; (2) identify patients at risk for complications and failures; (3) identify the most effective techniques and implant devices; (4) track implant usage; and (5) monitor and support implant recalls and advisories in cooperation with the U.S. Food and Drug Administration. The TJRR uses an electronic medical record (EMR) system to collect uniform data at the point of care. Data are abstracted from the EMR to the registry and followup data are collected through several methods.

Sponsor	Kaiser Foundation Health Plan
Year Started	2001
Year Ended	Ongoing
No. of Sites	350 surgeons at 50 medical centers
No. of Patients	140,000 total joint replacements

Challenge

The registry collects standardized total joint preoperative, operative, and postoperative data to supplement administrative data collected through the electronic medical record system. The registry database includes information on patient demographics, implant characteristics, surgical techniques, and outcomes. As a result, the registry provides opportunities for total joint replacement surveillance and monitoring, but the depth and breadth of the data make manual data reviews for adverse events (AEs) too resource intensive and time consuming.

Proposed Solution

Electronic screening algorithms were developed to detect AEs in the registry database in a timely, efficient manner. The algorithms use ICD-9 codes and CPT codes to identify complications of joint replacement surgery, such as revisions, re-operations, infection, and pulmonary embolism. All complications that are picked up by the screening algorithms are validated with a chart review. The screening algorithms are run and the results monitored on a regular basis to identify any trends.

The registry can also run specific queries to respond to physician concerns. For example, if physicians at participating medical centers notice a problem with an implant or hear about a problem from colleagues, they can request an ad hoc query of the registry database. The query can identify all patients receiving a particular implant and assess outcomes. In cases where the outcome of interest is not part of the registry database, the registry staff may perform additional followup through chart review. The staff may also check the Food and Drug Administration's Medical Product Surveillance Network (MedSun) to validate their findings against other data sources.

Once an implant has been recalled or when there is an advisory or concern, the registry can immediately generate a list of all patients who received that implant and notify their physicians. The registry can also identify complications and assess revision rates among its patients who received that implant. In addition, the registry staff monitors the outcomes of patients who received the implant through the revision surgery, death, or loss to followup.

Results

Since its launch in 2001, the registry has assisted participating physicians with their responses to several implant recalls and advisories. Data from the registry were used to identify surgical techniques that resulted in higher revision rates. The registry staff shared this information with physicians, resulting in reduced use of these techniques.

Key Point

Electronic screening algorithms offer an efficient method of identifying potential AEs in large datasets in a timely manner. For such algorithms to be effective, the registry database must collect detailed information on the implants' lots and catalog numbers, and must be updated frequently as new and modified products become available. In addition, when using medical codes, it is important to validate the results of the screening algorithm to ensure that coding errors have not affected the findings.

Case Example 57. Receiving Data from Medical Imaging Devices

Description	The Dose Index Registry collects data on radiation doses administered during computed tomography (CT) exams. Facilities can compare their average radiation dose for a particular exam (e.g., CT head exam) to that of similar facilities and to the national average. Such comparisons help facilities identify exams for which their dose indices may be higher than others and adjust their protocols accordingly. Because it does not collect patient outcomes, the registry is considered a registration registry rather than a patient registry. The example is presented to illustrate the ability to utilize medical devices to report information directly to registries or other databases.
Sponsor	American College of Radiology
Year Started	2011
Year Ended	Ongoing
No. of Sites	Over 200
No. of Patients	Over 1,000,000 CT exams

Challenge

Safety concerns over the effects of ionizing radiation exposure from diagnostic imaging have been described in numerous publications and summarized in a Joint Commission Sentinel Event Alert posted August 24, 2011 (Issue 47). To address some of these concerns, the American College of Cardiology established the Dose Index Registry to collect and compare data on radiation doses administered during CT exams.

For the data collection system to be a viable tool for participating facilities, it was imperative that the data be collected without interrupting the workflow at the facility (i.e., without adding additional workload for the CT technologist). The biggest challenge facing the registry was to automate and standardize the collection of dose information provided by several CT manufacturers in a variety of formats.

Proposed Solution

The sponsor worked with Integrating the Healthcare Enterprise (IHE) to develop the Radiation Exposure Monitoring (REM) profile. This profile describes the way dose information should be transmitted across different healthcare settings and specifies that information should be transmitted to a registry in the form of a Radiation Dose Structured Report (RDSR). However, only the most recent versions of CT

scanner models and software support RDSR. In order to accept dose information provided by older scanners, the registry developed software that could convert the data into the RDSR format. The software that collects dose information also removes patient identifiers before sending data to the registry.

The second hurdle in standardization was the development of a common nomenclature for CT exams. Different names are used for the same exam both within and among imaging facilities, and the registry needed a standard terminology for meaningful reporting. While it would have been possible to develop a new standard, the registry was aware of other lexicons under development, such as the Radlex Playbook. Conversations between the registry and the Radlex Playbook developers allowed the two groups to understand and meet each other's needs, and the registry was able to adopt the Radlex Playbook as the standard terminology for exam names. For facilities that submit data using non-standard terminology, these terms are mapped to Radlex Playbook terminology using a mapping tool developed by the registry.

Results

To date, the data collection system has collected information related to CT radiation dose from over 200 facilities nationwide and has collected dose information from over 1,000,000 CT exams. In addition to allowing comparison of dose indices between facilities, data collected from the registry will also be used to establish national benchmarks for CT dose indices.

Key Point

While not a patient registry, this example demonstrates that registries that collect information from medical devices may be able to reduce data entry burden by incorporating data transmitted directly from the device. When considering this option, registries may benefit from communicating with industry to find solutions that are not manufacturer-specific and can be implemented within a reasonable timeframe. Registries may also benefit from working with existing standards to determine if they can be modified to fit the registry's use case.

For More Information

http://nrdr.acr.org

Case Example 58. Combining Registry Data with EHR Data to Measure Real-World Outcomes of Implantable Devices

Description	Members of the Cardiovascular Research Network (CVRN) are conducting a longitudinal study of the characteristics, clinical outcomes, resource utilization, and costs among "real-world" patients receiving implantable cardioverter defibrillators (ICDs) for primary prevention of sudden cardiac death.
Sponsor	National Heart, Lung and Blood Institute (NHLBI), Agency for Healthcare Research and Quality (AHRQ), American College of Cardiology Foundation, Heart Rhythm Society

Year Started	2009
Year Ended	Ongoing (planned completion of outcome ascertainment in 2013)
No. of Sites	Seven health care systems, with 15 participating hospital partners
No. of Patients	3,600

Challenge

Implantable cardioverter defibrillators (ICDs) have revolutionized the approach to treatment for hundreds of thousands of patients in the U.S. with left ventricular systolic dysfunction who are at risk for sudden cardiac death. Despite broadened indications for ICD therapy, use varies across patient subgroups. Most existing data on complication rates, mortality, morbidity, and cost of primary prevention ICD therapy come from clinical trial samples, which enroll subjects who may not be representative of patients cared for in routine practice. Baseline data on patients and devices are available in the National Cardiovascular Data Registry's (NCDR) ICD Registry, but longitudinal outcomes are not routinely included in the registry system. Evaluation of longitudinal, real-world data is needed, but following large groups of patients in community care settings can present logistical challenges.

Proposed Solution

The Cardiovascular Research Network (CVRN) is a national research collaborative funded by the National Heart, Lung and Blood Institute (NHLBI) that leverages expertise, populations, and data sources from a consortium of 14 health plans in the U.S. Seven sites in the CVRN are currently sponsored by NHLBI, AHRQ, the American College of Cardiology Foundation, and the Heart Rhythm Society to conduct a longitudinal study of patients receiving ICDs for primary prevention of sudden cardiac death. The aims of the study are to (1) evaluate the extent to which patients receiving ICDs for primary prevention meet guideline-based eligibility criteria; (2) assess longitudinal outcomes, including complications, hospitalization, mortality, and delivery of device therapies among primary prevention ICD patients; and (3) identify the characteristics associated with these outcomes in real-world community practice. To achieve these goals, the study developed a new database, which links a national device registry with information from health system medical records archived in electronic and other forms.

Baseline information is obtained from the NCDR ICD Registry, which captures national data on primary prevention ICD implants for Medicare beneficiaries, although most participating hospitals, including the study facilities, submit data to the registry for all ICD recipients regardless of insurance status. Clinical and administrative followup data for three years post-implant are collected through the electronic health record (EHR) systems of the health plans participating in the CVRN. Finally, a new repository of arrhythmic episodes treated by ICD is being generated through review and abstraction of archived device followup records at the study sites.

ICD patients have periodic follow-up visits which include downloading data from their devices; this data can include the number and type of arrhythmic episodes detected by the device since the last check, what therapy (e.g. shock) was administered by the device, and the outcome of that therapy. The health systems download the device data from patients during an office visit or via remote transmission over the telephone. The device followup data are then incorporated into the health system medical record

archives. Since the study includes devices from a variety of manufacturers and includes device followup records in a variety of formats, study staff have created a standardized format for collecting therapy data so they can be adjudicated and analyzed. All three data sources are then combined into a single analytic dataset for addressing the study's specific aims, using a unique study identifier to link all data elements together for the same subject.

Results

The study includes 3600 subjects with primary prevention ICDs implanted from 2006 through 2010. Data collection began in 2009. A report on the study methods and the baseline characteristics of the study population has been published, demonstrating that important demographic and clinical characteristics of patients receiving ICDs in real-world clinical practice are significantly different from the population enrolled in the landmark clinical trials conducted on ICDs in the early 2000s.

Key Point

Existing registries and EHR data can be valuable data sources for measuring the long-term outcomes of devices in real-world settings. This is especially true for implantable devices, where data may be downloaded automatically from the device to an EHR system.

For More Information

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Chapter 24. Public-Private Partnerships

1. Introduction

As both government and private groups have shown increased interest in patient registries, public-private partnerships (PPPs) have become more common as a means to develop and support patient registries and data linkage projects. These types of partnerships may become more common, as recent legislative actions have suggested PPPs as a potential approach to registry development.[1] More information is needed on what types of public-private partnerships are possible, what issues should be considered when using such a partnership to develop or support a registry, and what characteristics and practices are likely to enhance the success of such efforts. This chapter defines PPPs in the context of patient registries, provides examples of existing PPPs, discusses considerations for setting up and operating PPPs, and reviews key factors for successful partnerships. While the discussion in this chapter primarily focuses on PPPs within the United States, some considerations for international partnerships are also reviewed. Case Example 59 offers a description of a public-private partnerships for registries.

2. Definition of a Public-Private Partnership

"Public-private partnership" is a broad term that refers to any partnership in which at least one entity is a public agency (e.g., a government entity) and at least one other entity is a private organization. The scope can range from partnerships at the local level, including local and regional health agencies, to national and international health agencies and other private institutions or organizations (e.g., professional associations, patient advocacy groups). A partnership implies some joint collaboration to achieve a common scientific goal. Partners may contribute intellectual capital, funding, data, or other services.

3. Public-Private Partnership Models

Public-private partnerships may take many forms. Some possible models include partnerships among Federal agencies to examine safety and effectiveness (e.g., INTERMACS); partnerships among health agencies from several countries on an international level to describe the clinical course of a disease and understand whether there are any effective treatments (e.g., Avian Flu Registry); partnerships with state agencies for quality improvement (e.g., Get With The Guidelines); and partnerships for evidence development for coverage decisions (e.g., Centers for Medicare and Medicaid Services). These models are described below, as case studies.

3.1. INTERMACS

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is the United States national registry for patients who have received durable, FDA-approved mechanical circulatory support device (MCSD) therapy to treat advanced heart failure. This registry was devised as a joint effort of the National Heart, Lung and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), clinicians, scientists and industry representatives. The goals of the registry are to:

- Facilitate the refinement of patient selection to maximize outcomes with current and new device options;
- Identify predictors of good outcomes as well as risk factors for adverse events after device implantation;

- Develop consensus "best practice" guidelines to improve clinical management by reducing short and long term complications of MCSD therapy; and
- Utilize registry information to guide clinical application and evolution of next generation devices.

A major challenge to INTERMACS was to create a registry with sufficient data quality, regulatory rigor, and sophistication to be able to achieve these goals. INTERMACS used the quality of a high-level clinical trial as its standard, realizing that it could never totally meet these standards but could emulate them as closely as possible in a structured, protocol-driven manner. See Table 30 for a listing of the regulatory, data quality, and scientific components of a clinical trial and which of these components are contained in INTERMACS.

Table 30. Regulatory, Data Quality and Scientific Components of a Typical FDA Clinical Trial and INTERMACS

	Typical FDA Clinical Trial	INTERMACS
DSMB/OSMB	✓	✓
Informed consent	✓	✓
IRB approval	✓	✓
Data use agreement	✓	✓
Human subjects training	✓	✓
Information security	✓	✓
Active website	✓	✓
Protocol	✓	✓
CLIA certification	✓	✓
Adjudication	✓	✓
Local PI certification	✓	✓
Data freezes	✓	✓
Audits	✓	✓
Complete enrollment	✓	✓
Complete data	✓	✓
AE definitions	✓	✓
Inclusion/exclusion	✓	✓
Nurse monitors	✓	✓
Site training	✓	✓
Site reports (QA, etc.)		✓
Standardized datasets	?	✓
Medical device reports to FDA	✓	✓
Mandatory data entry	✓	✓
Planned analyses	✓	✓
DAAP: research requests	?	✓
Annual meetings	✓	✓
Committees	✓	✓

Another major challenge to INTERMACS is to maintain focus on its mission while many tangential efforts and registry "by-products" have appeared. For example, INTERMACS has offered a new regulatory pathway for industry as FDA approval is sought for new devices. It also has provided the control arm for one FDA pre-market approval trial and is in the process of providing control data for

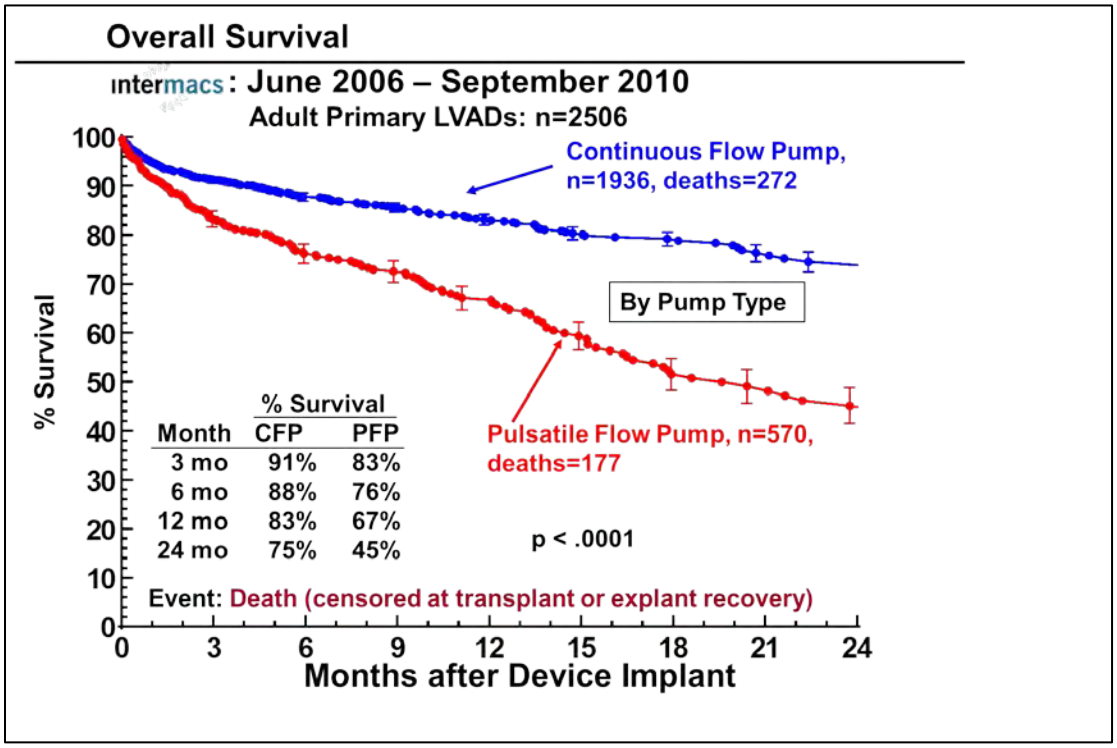
several ongoing and new trials. While these efforts were not part of the initial goals and contract deliverables of INTERMACS, they do, in general, fit the mission of moving the field forward.

In 2005, the original contract between NHLBI and the Division of Cardiothoracic Surgery at the University of Alabama at Birmingham (UAB) specified a target enrollment of 40 to 60 hospitals. As of July 2011, 120 hospitals have enrolled and have entered data on more than 5,000 patients.

The complexity of managing a patient with a mechanical circulatory assist device requires a similarly complex registry. Implantation of a left ventricular device, a right ventricular device, and/or a total heart replacement device must be captured along with subsequent device explants, multiple adverse events, functional capacity, and quality of life. The INTERMACS clinical research forms are numerous and detailed, with more than 1,500 data elements.

A unique feature of INTERMACS is that it is assessing a rapidly changing clinical and technological field. INTERMACS must be poised to quickly assess newly approved devices and to quantify the evolution in patient selection. Figure 13 shows survival based on two types of devices. These devices correspond to eras with the intracorporeal continuous flow pump being the most recently approved MCSD. The improvement in survival is dramatic, and INTERMACS has been the best way to quantify this improvement.

Figure 13. Overall Survival of Adult INTERMACS Subjects Receiving Primary Left Ventricular Assist Devices (LVADs), by Pump Type

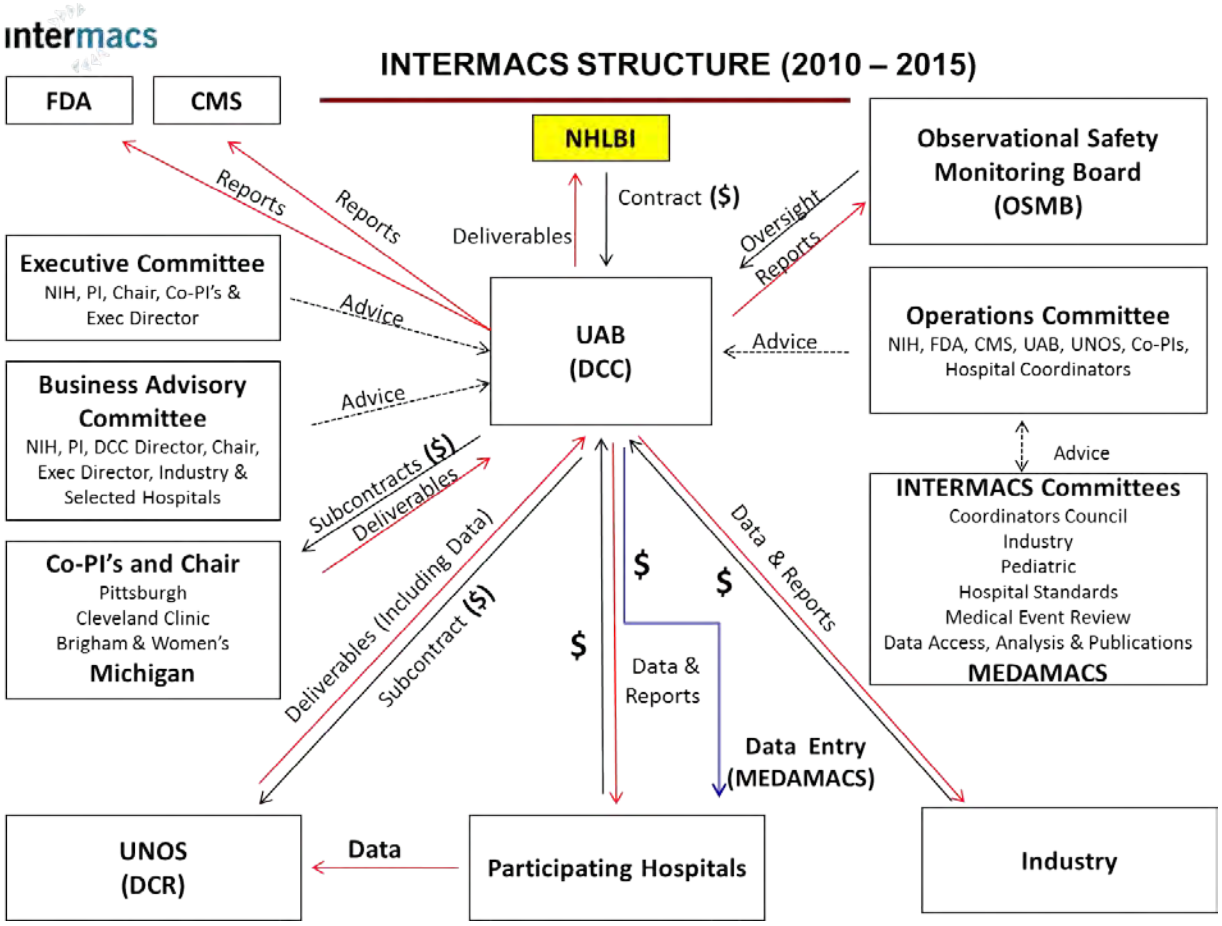


Initially, INTERMACS was the result of an NHLBI initiative in collaboration with FDA and CMS. Other stakeholders quickly joined in the planning stage, and they have continued to be INTERMACS partners. These multiple partners each have their own agendas and their own reasons for participating in

INTERMACS. While their goals do not always align, there is considerable overlap, and INTERMACS has been able to fulfill most needs for each partner. At the intersection of these agendas are the common goals of assessing current devices and contributing to the development of new devices by analyzing registry data. The ultimate goal for all of the partners is to improve patient outcomes.

Figure 14 is a schematic representative of the partners involved in INTERMACS. The relationships are necessarily complex and must be managed by clear expectations, deliverables, standard operating procedures, and lines of authority.

Figure 14. Structure of INTERMACS Partners



3.1.1. Stakeholders

NHLBI. As the sponsoring agency, NHLBI is both the primary partner and primary regulator of the registry. In addition to its oversight role, NHLBI has been involved in many of the day-to-day activities of INTERMACS, including the important role of ensuring scientific and regulatory integrity and patient protection.

FDA. Through their regulatory role in approving and monitoring new devices, the FDA functions as the "gatekeeper" for devices. INTERMACS benefited from early interactions with FDA in developing the

specifications of data elements and definitions of adverse events. As INTERMACS evolved, it worked with two separate components of FDA. The pre-market personnel at the Center for Device and Radiological Health (CDRH) helped create a registry that would build on the previous pre-market approval studies of MCSD. INTERMACS also worked with the post-market approval personnel of CDRH to explore ways to facilitate the analyses of approved devices. The partnership with FDA has evolved as INTERMACS has become a major post-market study vehicle for approved MCSDs, as evidenced by the collaboration with Thoratec and FDA to perform the post-market studies for HeartMate II, the first FDA-approved adult non-pulsatile pump.

CMS. When INTERMACS began, CMS was reimbursing hospitals for FDA-approved MCSDs that were implanted as destination therapy (DT) at approved centers. One of the requirements of the reimbursement was that data on implanted patients be entered into a national database. By the third year of INTERMACS, CMS changed the requirement to explicitly specify INTERMACS as the data repository and stated that a certified DT center must be in good standing with INTERMACS. This partnership with CMS has been critical to the development of a comprehensive database that captures the vast majority of approved durable devices implanted as DT or as bridge-to-transplant therapy.

Joint Commission. The Joint Commission is responsible for certifying hospitals as DT centers. INTERMACS collaborates with CMS, The Joint Commission, and hospitals to assist in the quantitative summaries necessary for certification.

Industry. Essentially every company that manufactures approved MCSDs or is in the process of gaining approval for an MCSD has been involved with INTERMACS. Industry was "at the table" during the meetings to develop INTERMACS. Many companies saw great potential for using INTERMACS in both pre-market clinical trials and post-market studies. The FDA has encouraged companies to work with INTERMACS. Some of these activities fall outside of the strict deliverables of INTERMACS but do fall within its goals.

Hospital Collaborators (Physicians, Surgeons, Coordinators, Administrators, and Quality Assurance Officers). The scientific and clinical energy of INTERMACS comes from physicians who care for heart failure patients and surgeons who implant the devices. The hospitals, via their coordinators, provide the data that populates the registry. INTERMACS serves as an important resource for the hospitals in activities related to mechanical circulatory support. For example, hospitals can submit requests for scientific studies, obtain their own electronic data from INTERMACS, and participate in an INTERMACS forum (the Coordinators Council) for coordinator feedback and discussion of relevant mechanical circulatory support topics. INTERMACS provides quarterly reports to participating hospitals that summarize and analyze their patients and provide benchmarking against registry-wide data. Patient-level reports that provide a chronological history of the patient's MCSD-related events are also available. These clinical summaries are an important tool in the data quality process.

Other Entities. In addition to the formal partners of INTERMACS, a number of other entities have requested collaboration. These include regulatory bodies of foreign governments, scientific societies, foreign hospitals, insurance companies, investment firms, and the media. Each request for collaboration is handled on an individual basis and considered within the framework of the goals and regulatory structure of INTERMACS.

3.2. Avian Flu Registry

Highly pathogenic infectious diseases continue to emerge, with substantial public health and financial tolls. Three features of newly emerged communicable diseases are immediately salient to registry development and use:

- Communicable diseases do not respect international borders.
- Communicable diseases, by their very nature, usually constitute a significant public health threat.
- Emerging communicable diseases usually enjoy a high media profile and are the subject of significant interest to the public.

Consider the recent H1N1 influenza pandemic and SARS as examples. While many newly emerged infections first manifest themselves in exotic or tropical locations, this is not an invariable rule, as shown by the emergence of legionellosis in Philadelphia.

The facility with which communicable diseases are able to cross international borders means they typically receive global attention, especially in our current era of mass international travel and globalization of trade. The fact that newly emerged infections usually represent a threat to public health means that governments and their agencies usually become involved in their investigation and management, typically at an early stage. Public concern, often fuelled by the media, may add to pressures upon public health authorities to react and to be seen as reacting to newly emerged threats. As a consequence, entities wishing to investigate newly emerged infections will generally need to engage with public health authorities, typically at a national government level.

A prime example of such a collaboration is the Avian Flu Registry, set up to investigate infection with influenza A/H5N1, a disease with almost 90% mortality if untreated.[2,3] The registry, which began in 2007, is a multi-country, observational study of the diagnosis, treatment, and outcomes of human cases of the A/H5N1 virus. Data are collected from health care professionals, and information abstracted from detailed, published case studies are also included. The registry has built a multinational, multicenter collaboration that houses the world's largest collection of human avian influenza cases and has made important contributions to understanding the treatment effectiveness for this highly lethal disease.[4,5] Its success has been built upon recognition of the unique nature of emerging infections, recognition of the differing needs of developing countries and collaborators, and adoption of a flexible and pragmatic approach. Its success is also attributable at least in part to the establishment of successful collaborations with national public health agencies in a number of countries.

However, the establishment of such collaborations is not always a straightforward matter, especially when initiated by the private sector. Newly emerged infections usually become politicized quite soon after their initial appearance. The classic example of this phenomenon is HIV, but SARS and pandemic influenza were also politicized rapidly after emergence. This politicization is seen in both economically developed democracies and developing countries. Further and deeper politicization may ensue when the newly emerged infection is viewed by afflicted countries as stigmatizing them in some way or is seen as a matter of national security; the response of some governments to avian flu exemplifies these types of responses. Similar reactions were seen in Indonesia with H5N1 and in China with the early stages of SARS. Developing countries may also be sensitive to the fact that their health care systems do not offer the same level of care as is available in developed countries. These countries may also lack developed disease surveillance systems and may feel uncomfortable at this lack being exposed.

Considering these sensitivities, the establishment of registries to study newly emerged infections may require a different approach to that typically adopted in other disease areas. An understanding of local sensitivities and a willingness to attend to local needs and to answer local questions will be helpful. An avoidance of a 'one size fits all' approach should also prove helpful, with flexibility to react to different countries in different ways being important. A useful guiding principle in the establishment of such multinational collaborations is to place the needs of the collaborator first, rather than the needs of the entity establishing the registry. While national public health authorities may well understand the altruistic nature of much global public health research, their constituencies remain local, and they are answerable to their local political masters and public. Working in this type of environment adds an additional layer of complexity, but this has to be successfully navigated if success is desired.

The Avian Flu Registry provides a good example of these political issues and how they might be surmounted. A complaint frequently heard when approaching ministries of health for collaboration was that such previous efforts had yielded little or no benefit to the participating country, with little or no feedback once collaboration had been agreed and data entry completed. The Avian Flu Registry, from inception, took pains to ensure prompt feedback to collaborators of data analyses and registry findings and to respond to requests from collaborators for further analyses in a positive and timely manner.

The funding for the Avian Flu Registry came from a pharmaceutical company that had a marketed product for treatment of seasonal influenza. Since hardly any information was available about avian influenza, the registry sponsor wanted to learn more about the illness with an eye toward understanding if their product would be effective for this more lethal flu strain. While some may see primary funding from industry as a disadvantage, the apolitical nature of this funding may actually have been advantageous. The relationship between the funder and the scientists charged with building the registry was clearly established at the earliest stage of planning and documented in a clearly worded binding contract. It was in the interests of the industry sponsor to step back from operational issues, allowing the investigators to build an international collaboration with the sole purpose of understanding the disease, with the expectation this would be done as efficiently as possible and with findings to be shared with all participants.

In addition, the registry was created in its earliest stages to conform to principles of good practice for registry science, including formal ethical review, a Steering Committee, and various other governance structures that proved useful throughout the program. A complexity of the registry was its broad global reach, which included collaborators from 13 different countries. The nature of regulations varied by country and by collaborator, but was in all instances compatible with the founding documents of the registry, as enshrined in the agreement between the industry funder and the investigators, and as presented to an independent ethics review board. A formal Memorandum of Understanding outlined all the key principles for data sharing, protection of privacy, ethical review, etc. Original documents guaranteed protection of the identity of individual reporting countries, a restriction that was later lifted by mutual agreement once it become apparent that country-specific factors like viral clade and barriers to access to care tempered treatment effectiveness. The Data Access and Publications Committee also proved to be useful in terms of providing a formal mechanism for recording, reviewing, and prioritizing research questions that were posed to the registry.

3.3. Get With The Guidelines®

Get With The Guidelines® is a hospital-based quality improvement program operated by the American Heart Association. The program aims to improve in-hospital care for patients by providing tools to support adherence to clinical practice guidelines. Hospitals pay a fee to participate in the program, which involves collecting and submitting data on patients. The program uses the data to generate benchmarking reports and to provide real-time feedback on adherence to the clinical practice guidelines. The program has been successful at demonstrating sustained quality improvement at participating hospitals.[6]

State-level departments of health also have an interest in improving quality at hospitals within their state. However, the development of a comprehensive quality improvement program is often not feasible given resource and staff constraints. In several cases, state departments of health partnered with the American Heart Association to sponsor hospitals in the Get With The Guidelines program. The state agencies paid the program fee for participating hospitals and, in return, received reports on hospital performance on a quarterly basis. Hospitals agreed to share their performance data, which the program would normally keep confidential, in return for receiving free access to the Get With The Guidelines program.

3.4. Centers for Medicare and Medicaid Services (CMS) Coverage with Evidence Development

In 2006, CMS issued a guidance titled "National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development"[7] that presented a new option for CMS when determining whether a drug or device would be covered under Medicare or Medicaid. In addition to the existing possible decisions of "no change in current coverage," "non-coverage," and "coverage without special conditions," CMS could now grant "coverage with special conditions," in which:

> "The medical evidence is adequate to conclude that the item or service is reasonable and necessary […] only under one or more of the following circumstances:
>
> a. The item or service is covered only for patients with specific clinical or demographic characteristics.
>
> b. The item or service is covered only when provided by physicians and/or facilities that meet specific criteria.
>
> c. The item or service is covered only when specific data are submitted in addition to claims data to demonstrate that the item or service was provided as specified in the [national coverage determination]."[8]

Registries are particularly suited to this type of prospective data collection. This new Coverage with Evidence Development (CED) requirement spurred the creation of multi-stakeholder registries to facilitate data collection for drugs and devices receiving CMS coverage conditional on evidence development. Aside from CMS, which provides the incentive for the data collection, major partners often include professional associations (who contribute scientific guidance) and industry (who contribute funding). Registries that have been created or adapted to meet CED requirements include the National Oncologic PET Registry (NOPR) for the use of positron emission tomography to treat certain types of cancers[9] and the ICD Registry for the use of implantable cardioverter defibrillators.[10]

4. Considerations for Setting up a Public-Private Partnership

4.1. Governance

A public-private registry is, by definition, a collection of stakeholders who have different purposes and agendas that hopefully overlap at the intersection of clinical science and improved patient care. In order to keep the registry focused, the registry needs a central authority. Often, this central authority is the Principal Investigator (PI), who oversees the registry and is responsible for developing consensus among stakeholders. The PI is also responsible for ensuring that the registry and the analyses of the registry data remain scientifically relevant and unbiased. The PI's scientific and operational oversight can be augmented by an Advisory Committee, which can include co-PIs and representatives from various partners in the registry (e.g., funding sources, reporting entities, or subcontractors that handle operational aspects of the registry).

4.2. Involving Patients

As with many other types of outcomes research, there is a growing trend to involve patients and patient advocacy groups in the planning and operation of patient registries. Working with patients brings certain unique considerations, and varying levels of patient involvement may be appropriate and/or feasible for different PPPs. For example, some diseases such as influenza A/H5N1 lack a cohesive patient population or advocacy group, because of the disease's rarity and high mortality rate. However, patients can offer valuable contributions to PPPs when it is feasible for them to do so, especially around such areas as user burden (e.g., when the registry is collecting patient-reported outcomes), registry feasibility and training and support needs.

4.3. Operational Decisions

Many registries are complex in nature with operational components including regulatory, financial, informed consent, data entry software, progress reports, periodic meetings, and scientific analyses. These registries are essentially small businesses that require intense day-to-day operations that should fall within a well-structured effort. The structure of the registry efforts should be clear, with well-defined lines of authority and responsibility. The structure should also have the flexibility to adapt to changing science and the changing national landscape of regulatory requirements, such as the evolving nature of the Health Insurance Portability and Accountability Act (HIPAA) constraints. A representative Operations Committee that meets regularly to review the ongoing progress of the registry and to address issues as they arise may be desirable. This group can make decisions by consensus rather than a formal vote, and documentation (i.e., meeting minutes) should be created and distributed to memorialize decisions and actions taken.

4.3.1. Plans for Transparency and Communication

Transparency and ongoing communication are vital to the success of any complex registry, especially one that is a public-private partnership. An important vehicle for transparency can be a registry's public Web site, which can contain regulatory documents including the protocol and user's guide (see http://www.intermacs.org). The public face of the Web site for the Avian Flu Registry contains the registry prospectus and information about data security, along with an updated list of published scientific articles and presentations (see http://www.avianfluregistry.org), including many of the actual posters and slide sets for public viewing. Other options for engagement, transparency, and communication include periodic public stakeholder meetings, newsletters, and e-mail listservs.

4.3.2. Dispute Resolution

Disagreements, or even disputes, are inevitable when a group of diverse stakeholders collaborate on a single registry. As with any complex endeavor, the key to symbiotic working relationships lies in the initial formulation of the goals and expectations of the registry and of each collaborator. The responsibility of mediation and dispute resolution can be assigned to a leader within the registry, such as a Study Chair or PI, or can be handled by committee, as in the Avian Flu Registry.

4.3.3. Data Security

The data contained in any registry must be managed according to strict rules for data security, which can include secure password-protected access to data entry, secure transmission of data, background checks on personnel, personnel training on data security, virus scans of all computers, off-site backup of data, etc. Anyone creating a new registry is strongly advised to collaborate with information security experts, who can lead the registry through the data security requirements and can create protocols for security breaches. Additional information on data management, data quality, and data security can be found in Chapter 11.

4.4. Data Ownership, Data Access, and Publications

As discussed in Chapter 7, ownership of registry data is a complex issue. In many registries, the registry sponsor owns the registry data. However, PPPs may have multiple sponsors and multiple stakeholders. Because of these complexities, it is important for the registry to specify clearly who will have rights to the registry data in registry partnership agreements and contracts.

4.4.1. Data Access

A related question is who has access to the data. While some registries may rely on a scientific advisory board or other governing body to handle data access requests, PPPs should consider a formal Data Access and Publications Committee (DAPC). A formal DAPC can develop policies and manage requests for data access in a transparent, consistent way that is agreeable to all stakeholders. All data access should conform to HIPAA regulations, informed consent documents, and data use agreements (DUAs) between contributing sites and the registry. Many entities may request access to registry data, including some listed below.

- ***Data provider or participating site.*** Typically, the DUA between the site and the registry specifies that the site can request to receive all of its own data at any time, but may not request identified data from another site.
- ***Registry sponsor.*** The registry sponsor owns the data and therefore has complete access to all data. When the registry ends, the entire database is often transferred to the sponsor.
- ***Regulatory agency (e.g., FDA, CMS).*** A government regulatory agency may request registry data to fulfill safety reporting requirements or other obligations. In particular, if a sponsor has a marketed product that is used by any patients in the registry, that sponsor is subject to mandatory safety reporting requirements (see Chapter 12).
- ***Industry.*** Pharmaceutical companies or device manufacturers may request data of patients who receive their products, or may request registry data to use as controls for a clinical trial.
- ***Investigators (within or outside the registry).*** Investigators may request registry data for a particular research project; each request should be reviewed by the DAPC so that only the necessary data elements for the research project are shared.

- ***Public.*** Although rare, data requests from the media or the public are possible. Any information released to the public by the registry (via newsletters, public Web site, or other methods) should be reviewed prior to release, to ensure that data confidentiality is not compromised.
- ***Standardized datasets.*** Some registries produce de-identified, standardized datasets that are available to researchers on a periodic basis. These datasets contain no PHI, no product or treatment brand names, and no site identifiers, and they are often constructed to provide the information believed to be most helpful to researchers. The actual content of these standardized datasets and the policy for distribution should be governed by the DAPC, with approval by the registry sponsor.

4.4.2. Process for Publications

As noted above, PPPs may find it particularly useful to form a DAPC to prioritize research projects and handle data access requests. The committee should meet regularly to formally review, prioritize, and evaluate the requests based on the potential to impact clinical practice and the amount of data available to answer the research question. The DAPC can also work directly with an Advisory or Operations Committee to identify and facilitate internal research projects that directly address the stated research goals of the registry.

4.4.3. Process for Analyses

Depending on available resources, a registry can either conduct analyses to support publications in-house, contract an outside agency to conduct analyses, or leave this task to the data requestors themselves. If an outside agency or data requestor will be conducting analysis on registry data, a secure mechanism should be in place for sending the data to them. The DAPC should retain oversight of these activities, especially those that are intended to be used for manuscripts submitted to peer-reviewed publications.

4.4.4. Formal Documentation of Roles and Responsibilities

Whether a registry resembles a traditional public/private partnership (i.e., a group of stakeholders who come together to create and fund a registry) or a more unusual structure (i.e., a series of contracts and subcontracts that have precise deliverables), each entity is a collaborator in the sense that each partner provides something to the registry and receives something from the registry. For example, each hospital participating in INTERMACS provides the local effort for participation and data entry. The hospital also pays $10,000 per year for participation. In return, the hospital receives many deliverables and benefits such as quarterly quality assurance reports, clinical summaries of each patient, electronic copies of their data, participation in research projects, and representation on the INTERMACS committees.

Because each entity may have numerous functions within a registry, it is important that roles and responsibilities be clearly defined and documented at the beginning of the registry. An Operations Committee can be charged with producing the roles and responsibilities document and updating it periodically as needed.

4.5. Funding

Registries can obtain their funding from a variety of sources. For example, INTERMACS was initially funded by a contract from NHLBI. During the second five year contract (December 2010 – November 2015), NHLBI asked UAB to develop a cost sharing plan that would allow NHLBI to significantly decrease their contribution while obtaining funding from private sources. The primary goal of this new

arrangement was to obtain the necessary ongoing funding in order to achieve sustainability. This transition in funding is not unique to INTERMACS. Changes in funding are particularly common in PPPs, where funding often comes from multiple sources. When funding sources change, it is often necessary to revisit the roles and responsibilities and data access policies to ensure that all stakeholders are represented appropriately.

4.6. Ethics

4.6.1. Conflicts of Interest

Because of the variety of stakeholders involved, a plan for identifying and managing actual and perceived conflicts of interest (COI) is essential. In this context, COIs can be financial or intellectual. The plan should clearly spell out the timeline and process for obtaining completed COI and financial disclosure forms from participating members and for reviewing and managing any potential conflicts, particularly given any unique working relationships with the federal government, academic institutions, or industry. The plan should also define what constitutes a problematic COI, and this definition should be reviewed on a periodic basis and revised, if needed. It is suggested that the PI, co-PIs, Study Chair, Operations and Steering Committee members, subcommittee members, and individuals named on the contract (including subcontractors and their staff) be required to complete annual COI forms. Once collected, the forms can be reviewed by registry staff and any conflicts forwarded to the Operations Committee for review. Any individuals that have a financial disclosure identified through the COI review process should declare it prior to participation in any scientific meetings, government meetings, presentations at sites, registry annual meetings, Steering Committee meetings, etc.

4.6.2. Informed Consent

The informed consent documents are key elements in determining the unique relationship between a patient's medical information and the ultimate use of this information in achieving the goals of the registry. The document must contain an explicit description of who will see what data and how confidentiality will be maintained. For registries with many partners as is common with public-private partnerships, it is desirable to have a common Informed Consent form. If a common form is not used, the reasons for the different forms should be documented and transparent to all key parties. The Data Coordinating Center (DCC) for INTERMACS created an informed consent template in collaboration with the NHLBI that contains the necessary elements as determined by NHLBI and the institutional review board (IRB) at the DCC. Chapter 8 discusses informed consent in detail.

5. Evolution of Public-Private Partnerships

Registries that are public-private partnerships may undergo many changes over the lifetime of the registry. The registry goals and roles of stakeholders may change, and new stakeholders may become involved. Registries that are not initially set up as public-private partnerships may later evolve into PPPs. The general topic of Registry Transitions is covered in a new chapter, but there are several changes and transitions that are unique to public-private partnerships.

For example, INTERMACS began as a collaboration between NHLBI, FDA, and CMS. The other partners currently involved in INTERMACS (and shown in Figure 14) joined later, and each brought their own agendas and goals for the registry. As these new partners joined, INTERMACS had to evaluate the many different goals they brought to the table, identify areas of overlap, and determine how

INTERMACS could meet the needs of each partner while remaining focused on the ultimate goal of the registry: to improve patient outcomes.

Sometimes a registry is not initially organized as a public-private partnership and later evolves into one. This often happens when potential stakeholders do not see the value of being involved in a registry in the beginning stages, particularly when the registry has not yet published any results or provided proof of concept. In these situations, it is incumbent on the registry originators to operate the registry and produce results that will entice stakeholders to participate. For example, the Avian Flu Registry (funded by industry and operated by a private contract research organization) found much more success in partnering with international ministries of health after the Registry published its results in peer-reviewed journals and presented abstracts at well-known scientific conferences. Similarly, Get With The Guidelines was able to partner with state-level health departments only after consistently demonstrating its success in improving patient quality of care.

6. Considerations for Managing a Public-Private Partnership

6.1. Stakeholder Engagement

Once a public-private partnership has been established, it becomes critical to focus on proper management of the project. Major stakeholders may be involved, including clinicians, payers, patients/consumers, federal agencies, and industry/manufacturers. Inclusion of varying perspectives ensures balance, yet decision-makers from different sectors may have conflicting priorities. Engaging each of these groups with the common goal of improving health care quality and patient outcomes through sharing of data and other resources is vital to the achievement of the partnership. Such collaborations have occurred successfully in several industries where no single entity had the resources or expertise to drive an entire field.[11,12] Eliciting trust among decision-makers combined with advice and/or participation from reputable associations are valuable incentives for maintaining the interest and engagement of collaborators.[13,14,15] Successful collaborations satisfy the needs of multiple stakeholders, providing immediate value and long-term returns, while driving innovation and efficient productivity and leading to the development of best practices.

Setting appropriate expectations for the participation of each group within the partnership is also vital. The utility of pre-project meetings involving discussion of priorities and policies that will govern the collaborative efforts cannot be overemphasized.[16,17] Roles and responsibilities must be clearly defined and mutually agreed upon so that all stakeholders benefit equally.[18] Evaluation of the available literature may reveal which practices have worked for other partnerships. Establishing guidelines that dictate partnership activities, including conflict of interest procedures, will allow accountability.[19,20] Identification of a PI with strong leadership skills, a project manager to drive timelines, and other properly-trained team members will ensure successful execution of project goals.[21] Agreement between participating groups on the time commitments required of them from the beginning will help set appropriate expectations. Resources that increase ease of communication and minimize time commitments, such as shared websites or databases,[22] can speed development and improve participation. Although the importance of timelines is paramount, the ability to be flexible is also important in the changing landscape of healthcare policies and for public-private partnerships that add partners and collaborators and adapt over time.[23]

6.2. Communication

Communication tools for generating and maintaining interest among stakeholders and participants are beneficial when used effectively. Initiation of interactive workshops or exchange forums between public and private sectors, dissemination of publications and news releases, and updates at professional meetings are all effective ways of communicating the necessary information to drive the partnership forward.[24] Periodic updates and exchanges of data have been shown to have positive effects on collaborations.[25] Overly frequent distribution of printed communications, required teleconferences, or excessive meetings will generate unwanted frustration or lack of continued support/participation. However, the value of a reasonable number of written updates, fairly regular calls (monthly, for example), and at least two in-person meetings (at onset and before distribution of results) are essential for building strong team morale, maintaining commitments, and achieving successful outcomes. Clearly these processes must be adapted to accommodate national and regional cultural sensitivities.

6.3. Visibility

Visibility of results and the breadth of dissemination of information obtained through the partnership should be discussed in the early planning phase of the project. Preparing results for wide dissemination requires considerable time and effort, which may not fall within the scope of the project team. However, if such a distribution is desired and the funding and resources are available, the results can benefit a more widespread audience. Visibility of potential and perceived conflicts of interest should also be discussed at the onset of the partnership. An internal and/or external monitoring committee can reinforce ethical standards and trust among stakeholders.[26] The priorities involved with transparency and diffusion of information will depend on the nature of the partnership, the initial agenda, and the resources available.

6.4. Change Management

Anticipating and planning for change is good practice for all patient registries. Because of the nature of public-private partnerships and the variety of stakeholders involved, PPPs in particular may be more subject to changes in registry goals, stakeholders, budget, processes, and other areas. For this reason, it is important for PPPs to have a plan for how change will be managed. Tools that can assist in change management planning include a manual of procedures, a governing body, infrastructure for ongoing personnel training, and a plan for communicating change.

Protocols, governance and other related documents may change from time to time as a registry matures and adapts. Documents should be reviewed periodically and updated as needed. Re-submission for ethical review may be required, depending on the extent of the changes. The use of versioning (e.g., naming a protocol "Registry Protocol v1.0") can reduce miscommunications and ensure that all stakeholders refer to the same document. It is also important to document major decisions that will affect the scope, budget, or otherwise impact the registry and share information about these decisions with key stakeholders. For more information on managing change in registries, see the Chapter 11.2.6 and 14.

7. Special Considerations for International Public-Private Partnerships

International PPPs face some unique challenges, in addition to the usual challenges of language and cultural barriers. While some investigators may complain about the burden of compliance with regulation in developed countries, the opposite problem may exist in some less developed jurisdictions. The absence of a clear regulatory framework within which to operate may create problems in both the investigator's home country and in the host collaborating country. One example may be lack of clarity in determining

the responsible office for establishment of collaborations; another example may be changes in the local political landscape that alter this locus of responsibility. An issue that should be clarified in advance is the right to publish findings and to confirm the authorship. Early attention to these details will avoid later issues.

8. Key Factors for Success and Potential Challenges

8.1. Key Factors for Success

A PPP represents a valuable business model for the development of multi-stakeholder registries. The shared-risk and shared benefit nature of PPPs presents an ideal opportunity for attracting involvement from risk-averse elements in any sector, but these benefits coincide with challenges that may derail the success of a project as a whole.

A PPP starts with an identified public health issue in need of a solution. There is no shortage of strong, scientifically valid and important topics relating to the delivery of medical care and use of medical products; the challenge is in prioritizing these issues and focusing on pragmatic solutions for high-impact projects. For example, a registry tracking care patterns for a well-understood rare disease would likely generate less support than one that would collect acute and chronic data on a novel treatment for a highly prevalent condition. To ensure success of a given PPP, it is vital to communicate with a broad array of stakeholders early in the process to assure that the problem is appropriately conceptualized and that the goals mesh with priorities of stakeholders.

While PPPs represent a variety of interests and viewpoints, the value of a strong leader cannot be overstressed. Because of the nature of professional life, few people have the necessary time to devote to the difficult task of managing not only the scientific aspects of developing a registry, but also the equally challenging task of developing and managing an interdisciplinary team with diverse interests toward a common goal. The presence of a trusted and dedicated individual who is willing to commit substantial time to the development of a PPP is critical to the success of the project. This individual needs to be a recognized expert voice and have skills as a moderator, mediator, business developer, and salesman. Individuals who are open to pragmatic approaches that accommodate stakeholders without sacrificing the scientific integrity of the project will have a high likelihood of success. Similarly, an active and dedicated core team that represents an array of stakeholders is also necessary to support the goals of the PPP.

Many PPPs, like any project, are started with small conversations that grow into grand ideas. The formative stages of a PPP involve many steps of developing and refining the issues and potential solutions long before the first data entry form is ever filled out, and often consist of preparing documents, attending calls, holding workshops, and other collaborative activities. While talk is indeed cheap, there comes a point where the project cannot move further without some substantial funding. It is good practice to begin development of a funding strategy early, often alongside the development of the scientific strategy. Funding options should not depend solely on any one source or sector. This approach broadens the base of support, making it more likely to be a sustainable funding model, while having the added benefit of potentially reducing the appearance of conflicts of interest.

If one views the PPP as a business model, the necessity to provide accurate and timely reports to shareholders becomes more readily apparent. In the planning process and throughout the development of the project, it is important to set goals and produce meaningful deliverables within a reasonable time

frame. Projects that appear to drag on, or that have a dearth of outputs for an extended period are likely to lose support and jeopardize funding. Likewise, reporting of the progress of a project is critical to sustain interest and support. For PPPs that involve professional or academic societies, the annual scientific sessions of these organizations often provide an ideal opportunity to update the community.

Clear communication in open forums that encourages and allows for buy-in and feedback is another critical component to ensuring success in a PPP environment. A registry is a unique application of the PPP model in that successful implementation of the final project is heavily dependent on individual hospitals and practitioners. Having stakeholders represented at the leadership levels of organizations is necessary for good governance; however, communicating with the physicians, hospitals, nurses, and associated staff to address their concerns will promote enrollment. Further, the case must be made to this group that the registry will add value to their organizations, and not just represent a further drain on their already sparse time.

Some registry characteristics that increase the probability of success include:

- The registry should have goals that address a clear and current clinical need in a well-defined population. These goals become the rallying point for the diverse partners.
- The expectations of each partner should be explicitly numerated, pragmatic, transparent, and measurable.
- The registry should return value to all partners who are financial contributors. As much as possible the value should equal or exceed the financial contribution for each partner.
- The registry should have strong, respected leaders who have national or international reputations. Mutual respect among all partners is also necessary for a strong working relationship.
- High quality data is essential to the success of the registry. Data must be collected consistently, using agreed-upon definitions. Protocol-driven efforts to assess compliance with the registry protocols and well-defined efforts to repair any deficient areas are critical.
- While the registry should be built for consistency, it still must have an element of flexibility to allow it to react to changes in the clinical landscape.
- The registry should have policies and procedures in place to support transparency and ongoing communication to partners and participants

8.2. Common Challenges

The first challenge is involving stakeholders in designing the registry and implementing the registry procedures (e.g., governance, operational management, analysis). The second challenge is creating a data collection plan and registry procedures that are realistic and will capture the data necessary to meet the goals, but flexible enough to accommodate change when necessary. The third challenge is adhering to the registry procedures and data collection plan. If a registry is successful, many spin-off projects and additional uses of the registry may appear. Maintaining focus on the original goals of the registry while responding to increasing registry demands is clearly a challenge. Creating a business plan that will allow for sustainability of the registry is one of the biggest challenges. Assessing quality of life and other patient-reported outcomes, including clinical assessments (e.g., neurocognitive assessment) is a challenge because direct interaction with the patient is required. The biggest challenge is to provide daily high-level effort that simultaneously focuses on regulatory and data quality issues while continuing the scientific mission of the registry.

9. Summary

Public-private partnerships are increasingly being used as a model for operating patient registries in the U.S. and internationally. Government regulators and payers are increasingly requiring evidence development to inform decisions about approval, coverage, and expanded indications, and patient registries governed by public-private partnerships are in a unique position to fulfill those requirements. In the future, PPPs that include international partners will continue to be important. While there are special considerations for planning and operating public-private partnerships, they offer a unique way for varied stakeholders to contribute their particular strengths to achieve a common scientific goal.

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Case Examples for Chapter 24

Case Example 59. Developing a Public-Private Partnership for Comparative Effectiveness Research

Description	The Registry In Glaucoma Outcomes Research (RiGOR) is a prospective observational study comparing the effectiveness of treatment strategies for open-angle glaucoma.
Sponsor	Agency for Healthcare Research and Quality (AHRQ)
Year Started	2011
Year Ended	Ongoing
No. of Sites	47 community and academic ophthalmologic practices
No. of Patients	2,625

Challenge

In 2009, the Institute of Medicine disseminated a landmark report, "Initial National Priorities for Comparative Effectiveness Research", which listed research priorities for the newly enacted American Recovery and Reinvestment Act (ARRA). Among the 100 priority research topics identified was evaluating the different treatment strategies for primary open-angle glaucoma (POAG). Since POAG disproportionately affects African-Americans, understanding the effectiveness of treatment strategies in minority populations was also of special interest. With ARRA funding, AHRQ sought to develop high-quality scientific evidence to inform decisionmaking by clinicians and patients. An approach was needed to obtain continued and expanded input from the various stakeholders while addressing existing evidence gaps.

Proposed Solution

A diverse group of stakeholders was assembled to implement the registry, provide scientific guidance, and develop dissemination plans and further key research based on study findings. The principal investigator and co-principal investigators represent AHRQ, the American Academy of Ophthalmology (AAO), the University of California at Los Angeles (UCLA) Jules Stein Eye Institute, and the Outcome DEcIDE Center. AHRQ provides oversight and financial support to the project, with scientific leadership from the principal and co-principal investigators; the Outcome DEcIDE Center manages the operational aspects of the study; AAO and UCLA engage sites and investigators and provide guidance on clinical issues. The stakeholder committee is comprised of individual clinical advisors and representatives from the Glaucoma Research Foundation, American Glaucoma Society, National Medical Association, and state-level health care organizations.

Developing the study protocol, initiating start-up activities and decisions, and analyzing and reporting the findings require continued communications among all stakeholders. A communication plan was developed to outline project team roles and organizational structures for each stakeholder. Regular stakeholder committee meetings have created a forum to discuss design issues, share study status,

solicit input on unexpected challenges, and discuss future research. Site and patient recruitment efforts were designed to maximize geographic diversity and enrollment of minority populations. Quarterly study newsletters and investigator meetings coinciding with the AAO annual meeting were also implemented to maintain site interest.

Results

Launched in 2011, RiGOR is a prospective, observational cohort study designed to compare the effectiveness of treatment strategies for POAG. Different treatment strategies studied in the registry include laser surgery, other procedures (such as incisional surgery or other glaucoma procedures), and medications. All treatment decisions are at the discretion of the treating physician according to their usual practice. Data collection includes patient demographics, medication, visual measures, glaucoma severity, surgical characteristics, adverse events, and patient-reported outcomes, and occurs at baseline, 3 months, 6 months, and 12 months.

The registry has been successful in meeting its objective of enrolling a high percentage of minority patients. An interim report describing baseline findings is currently in process, and full analyses are expected to be published in 2013. The current AHRQ funding will allow RiGOR to operate through 2013. A future challenge for the registry will be identifying and transitioning to a new funding source once the initial funding ends.

Key Point

The public-private partnership model can be an effective approach to engaging multiple stakeholders in an effort to address a comparative effectiveness research question. When working with multiple stakeholders, it is critical to clearly identify roles and communicate regularly with all stakeholders to address any design, operational, or analytical issues, solicit input from all contributors, share study findings, and maintain stakeholder engagement.

For More Information

http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=841.

Section VI. Evaluating Registries

Chapter 25. Assessing Quality

1. Introduction

As described throughout this guide, registries are created for many purposes, including scientific, clinical, and policy. Registries may also serve more than one purpose and potentially may add or change purposes over time. This leads to variations in design, operations, or quality assurance that are sometimes viewed as methodological inadequacies. It is not generally appreciated that the attributes that are important for some purposes may be less important for others. As a result, it is important to distinguish these purposes with respect to recommending particular practices.

For example, in describing a very rare disease or small subgroup of patients for whom there is little other information, some relevant data from a registry are better than no data. Further, even registries that fall short of including many of the essential elements of good registry practice described in this chapter may still provide valuable insights for some purposes. As a general rule, quality should be evaluated by elements that directly impact the ability of the registry to achieve its main objectives.

A registry must be fit for its purpose, with essential items covered for all registries. Nonetheless, while all registries can provide useful information, there are levels of rigor that enhance validity and make the information from some registries more useful for guiding decisions than others. For example, there are certain practices that enhance the validity and reliability of registries intended to evaluate safety and comparative effectiveness.

Prior to the publication of the first edition of this user's guide,[1] no criteria had been developed by which to guide evaluation of registries. Research into the quality aspects of registries, whatever their purpose, remains relatively sparse, especially when compared with the rich information available to guide quality in clinical trials. The aim of this chapter is to provide a simple and user-friendly listing of attributes and practices that allow registries to be described and evaluated for their essential elements and enhancements in the context of the purpose for which they are conducted. Information is presented to help distinguish between:

- Essential registry practices that are desirable for every study.
- Practices that could enhance scientific rigor and that are particularly important for certain purposes, but may not be achievable because of practical constraints.

The items listed as "essential" elements of good practice are applicable to all patient registries. While it may not be practical or feasible to achieve all of the essential elements of good practice, it is useful to consider these characteristics in planning and evaluating registries. It is also important to remind readers that some of the fundamental differences between clinical trials and registries affect how quality is evaluated. For example, a clinical trial will have a schedule of visits and assessment that is rigorously maintained. A clinical trial patient who does not adhere to the schedule may be viewed as noncompliant with the protocol and could potentially be discontinued from the trial. In a registry, treatments and

assessments may be recommended, but the registry participant who does not adhere to the schedule typically is allowed to remain in the registry, and this is considered good practice. Moreover, some argue that the kind of data that are produced by registries may be more valid for inferences needed in clinical decisionmaking because few exclusion criteria are used and inferences are drawn from measurements customarily used by clinicians.[2]

The information described in this user's guide, and particularly in this chapter, is also designed to be used in reporting registry study results, much as CONSORT (Consolidated Standards of Reporting Trials) guidelines have been used to improve reporting of clinical trials,[3] and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines are being used for observational studies.[4,5]

2. Defining Quality

This chapter has adapted a definition of *quality* that was developed for randomized controlled trials;[6] the term is used to refer to the confidence that the design, conduct, and analysis of the trial or registry can be shown to protect against bias (systematic error) and errors in inference—that is, erroneous conclusions drawn from a study.[7] As used here, quality refers both to the data and to the conclusions drawn from analyses of these data. For more information about the types of biases that can affect observational studies, as well as strategies for addressing and even avoiding these biases to the extent feasible, see Chapters 3 and 13. For more information about bias, validity, and inference, readers are encouraged to consult epidemiologic textbooks.[8,9,10,11]

3. Measuring Quality

There are two major difficulties with assessing quality in registries:

- It can often be difficult to differentiate between the quality of the design, the study conduct, and the resultant information available.
- There is a lack of empirical evidence for evaluating the parameters purported to indicate quality and their impact on the utility of the evidence produced from registries.

Evaluations of the quality of any registry must be done with respect to the essential elements of the registry and those aspects that are important in the context of the registry's main purpose and the purpose for which the data are being used. Both the internal and external validity of the data must be taken into account along with considerations of cost and feasibility.

The most commonly used method to assess quality of studies is a quality scale; there are numerous quality scales of varying length and complexity in existence, with strong views being expressed both for and against their use.8(p. 135-61),12,13 Different scales emphasize distinctive dimensions of quality and therefore can produce disparate results when applied to a given study. In most situations, a summary score is derived by adding individual item scores, with or without weighting. This method, however, ignores whether the various items may lead to a bias toward the null (suggesting the erroneous interpretation that there is no effect) or tend to exaggerate the appearance of an effect when none really exists, and the final score produced does not reflect individual components.[14] Furthermore, validation of the scales is difficult; studies have found wide variation in the scores for a particular study both by different reviewers and the same reviewers at different times.[15]

The approach suggested here is to undertake a quality component analysis, which involves an investigation of the components that may affect the results obtained. In the quality component analysis, a differentiation is made between two domains: research quality, which pertains to the scientific process (in this instance, the design and operational aspects of the registry), and evidence quality, which relates to the data/findings emanating from the research process.[16,17,18] According to Lohr,[16,17,19] "[t]he level of confidence one might have in evidence turns on the underlying robustness of the research and the analysis done to synthesize that research." The individual items highlighted as essential elements of good practice and evidence quality can be used to guide the evaluation of registries, though there are no criteria as yet as to what proportion of elements must be satisfied in order to be considered "good enough" for various purposes.

To select the quality components for analysis, several key elements identified in previous research studies, among many consulted, were Guidelines for Good Pharmacoepidemiology Practice,[20] the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guideline on Good Clinical Practice,[21] the Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Ethical Review of Epidemiological Studies,[22] standards developed for the conduct of registry studies for patient-centered-outcomes research,[23] various reports on rating scientific evidence from observational studies[13,24] and surveillance systems,[25] Goldberg's review of registry evaluation methods,[26] the MOOSE (Meta-analysis of Observational Studies in Epidemiology) proposal,[27] the EULAR (European League Against Rheumatism) task force on biologic registers,[25,28] and Guidance for Reporting Observational Studies maintained by the Equator Network.[29] Special purpose quality guidance documents, including the GRACE principles for observational studies of comparative effectiveness (see www.graceprinciples.org),[30] were also reviewed.

The results of the quality component analysis must be considered in terms of the registry purpose and in the context of the disease area (See Table 31.) For example, a disease-specific registry that has been designed to look at natural history should not be deemed low quality simply because it is not large enough to detect rare treatment effects.

Table 31. Overview of Registry Purposes

- Determine clinical effectiveness, cost effectiveness, or comparative effectiveness of a test or treatment, including evaluating the acceptability of drugs, devices, or procedures for reimbursement.
- Measure or monitor safety and harm of specific products and treatments, including comparative evaluation of safety and effectiveness.
- Measure or improve quality of care, including conducting programs to measure and/or improve the practice of medicine and/or public health.
- Assess natural history, including estimating the magnitude of a problem; determining the underlying incidence or prevalence rate; examining trends of disease over time; conducting surveillance; assessing service delivery and identifying groups at high risk; documenting the types of patients served by a health provider; and describing and estimating survival.

4. Quality Domains

The quality domains shown here reflect the domains described earlier in this user's guide and have also been adapted from work undertaken for clinical trials. For research, the quality domains are research design and processes and procedures, which address planning, design, data elements and data sources, and

ethics, privacy, and governance. Table 32 shows the essential elements of good registry practice for research, and Table 33 shows optional indicators of quality that may enhance registry validity and reliability, subject, of course, to feasibility and applicability.

For evidence, the quality domains are external validity, internal validity, and analysis and reporting. Table 34 shows the essential elements of good registry practice for evidence, and Table 35 shows optional further indicators of quality, including those important for selected purposes. It is important to weigh efforts taken to promote the accuracy and completeness of evidence in balance with the public health urgency of a problem, the types of interventions that are available, and the risks to public health from coming to a wrong conclusion. These lists of components are most likely incomplete, but the level of detail provided should be useful for high-level quality distinctions.

Most importantly, the essential elements of good practice, as well as the optional further indicators of quality depend, to a great extent, on the resources and budget available to support registry-based research.

Table 32. Research Quality—Essential Elements of Good Practice for Establishing and Operating Registries

Research design • Develop objectives and/or research questions (main and supporting, as needed). • Identify the target population, eligibility, and inclusion and exclusion criteria. For registries where practice characteristics may influence outcome, seek to include diverse clinical practices. Where possible, a broad range of patients (few exclusion criteria) is desirable to facilitate subgroup analysis. • Identify important personal identifiers, exposures, risk factors, and mitigating (or protective) factors, and seek those that are reasonably feasible to collect. Use the literature to inform the choice of data elements. • Choose outcomes that are clinically meaningful and relevant to patients and to the medical community for decisionmaking. Define patient outcomes clearly, especially for complex conditions or outcomes that may not have uniformly established criteria (e.g., define "injection site reaction" in operational terms). Consider whether these outcomes will be collected from medical care providers, patients or other observers. • Use validated scales and tests when such tools exist for the purpose needed. • Understand the followup time required to detect events of interest and whether or not the objective is feasible to achieve. Ensure that the followup time planned is adequate to address the main objective. • Plan the main analyses, including specification of exposure and effect measures. • Consider the size required to detect an effect should one exist, or to achieve a desired level of precision. Consider whether or not the sample size requirement can be achieved within the available time and budget constraints. • Consider the most efficient and reliable means to consistently collect data of sufficient quality to meet the registry's purpose and whether existing data can be used to supplement or minimize active data collection. • Plan to report safety events according to regulatory requirements. • Plan the data analysis to address the key objectives or research questions, including what comparative information, if any, will be used to support study hypotheses or objectives.
Processes and procedures • At the outset, reach agreement on key aspects of the registry and document them, including the goals, design, target population, methods for data collection, data elements and sources, high-level data management and data quality review, and how human subjects will be protected. It may be helpful for stakeholders to have input to assure clinical relevance and feasibility.

- Establish a process for documenting any modifications to the plan, since the main objective may change over time as knowledge accumulates, and the plan for data collection and followup may need to be adapted.
- Carefully consider the issues of protection of human subjects—including privacy, informed consent, data security, and study ethics—and address them in accordance with local, national, and international regulations. Obtain review and approval by any required oversight committees (e.g., ethics committee, privacy committee, or institutional review board, as applicable). If linkage of registry data to other sources is planned, consider the additional issues of protection of human subjects.
- Define the role of any external sponsor, including data access and use.
- Provide clear, operational definitions of outcomes and other data elements. Establish a data and coding dictionary to provide explicit definitions and to describe coding used. Whenever possible, use standardized data dictionaries, such as the International Classification of Diseases, and use coding that is consistent with nationally or internationally approved coding systems to promote comparability of information among studies.
- If linkage of registry data to other sources is planned, consider any additional requirements that may influence successful linkage, such as selection of data elements and definitions used.
- Plan subject and physician recruitment targets and methods to achieve those targets, and plan the means for monitoring enrollment and retention.
- Plan to expend reasonable efforts to ensure that appropriate patients are enrolled systematically and followed in as unbiased a manner as possible.
- Identify appropriate personnel and facilities, including those for secure data storage. Identify the individual(s) responsible for the integrity of the data, computerized and hard copy, and make sure these individuals have the training and experience to perform the assigned tasks.
- Develop standard instructions for use in training data collectors. For safety studies, create a process for identifying and reporting serious events that is consistent with regulatory requirements. Plan training for study personnel about how to identify serious events, including:
    - Asking about complaints or adverse events in a manner that is clear and specific (e.g., solicited vs. unsolicited).
    - Knowing if and how information should be reported to manufacturers and health authorities.
- Create a quality assurance plan that addresses data editing and verification. Plan an approach for handling missing data (e.g., go back and collect those data or make a plan as to how "missing" data will be coded in the data files.)
- Anticipate how study results will be communicated on completion.

Table 33. Research Quality—Further Indicators of Quality for Establishing and Operating Registries (Optional)

Research design

- Formalize the study plan as a research protocol.
- For comparative effectiveness and safety,
    - Use concurrent comparators, since they may offer an advantage over historical or external comparison groups, especially in situations where treatments are evolving rapidly. The comparator cohort should be as similar as possible to the exposed cohort, aside from the exposure under study, and should reflect current clinical practice.
    - Use formal statistical calculations to specify the number of patients or patient-years of observation needed to measure an effect with a certain level of precision or to meet a specified statistical power to detect an effect should one exist, although the desired size may not be achievable within the practical study constraints. Temper considerations about precision and power with budgetary and feasibility constraints, while also giving heed to the importance of conducting research in areas where little exists.

- Develop formal analysis plans.
- Collect information to permit linkage (and therefore validation) with external databases such as the National Death Index, electronic health records, or claims datasets, as appropriate.
- Post the registry on a public registries or trials listing registry, e.g., at ClinicalTrials.gov.

Processes and procedures

- Undertake a feasibility study or pilot test, e.g., when studying hard-to-reach populations, when sensitive data are sought, and when critical registry methods are new or have not otherwise been tested.
- When capturing composite scores, collect and record core components, if possible.
- Collect information on start and stop dates of treatments of interest and dose (if relevant) or other means to discriminate between high and low exposure.
- Use similar methods of followup for exposure and comparison cohorts, and for all subjects in each cohort, to the extent feasible.
- To enhance transparency, consider using an advisory board, particularly a board that includes members who are external to the clinician, center, or company that sponsors the research. An advisory board or steering committee can promote clinical and public health relevance and may assist with governance and communication. If using an advisory board, consider rotating membership and/or term limits.
- Specify publication policies in advance of collecting data and reevaluate at regular intervals (e.g., annually).
- Develop a plan for stopping or transitioning the registry, including any archiving or transferring of data and notifying participants, as appropriate.
- Consider when and how to allow third parties access to data, if feasible, and the process for any such data access.
- For safety and comparative effectiveness,
    - Data collection methods should not limit site participation to the extent that the representativeness of sites is compromised. Although a single method of data collection is most efficient, multiple methods of data collection may be desirable for some purposes.
    - Loss to followup should be monitored and characterized to ensure that followup is sufficiently complete for the main objective and to see if there is differential loss to followup by characteristics that may affect the likelihood of achieving the main objectives. Reasonable resources should be devoted to minimizing loss to followup.
    - Quality assurance (QA) may include review or monitoring of a sample of data and/or data review by an adjudication committee for complex conditions or endpoints for which established procedures and/or coding are not used. For most purposes, a risk-based strategy should be used for QA, focused on detecting and quantifying the most likely causes of error and the types of error most likely to affect the registry purpose, with QA activities adapted based on observed performance (e.g., increase QA for sites that appear to be having difficulty in study conduct or data entry).
- For safety, comparative effectiveness and quality improvement,
    - Appropriate documentation should be maintained, such as an audit trail, to ensure proper handling of information and to support transparency.
    - Establish processes and standards for creating analytic data files and maintaining such files to support publications and presentations, since registry analyses may be performed on live data (data that may change as the registry continues to collect and verify information through various quality control procedures) or on data that have been locked and have undergone formal review and editing.
    - Use open standard approaches to interoperability when health information systems are used for active data collection to permit more efficient collection of data from multiple systems.

Table 34. Essential Indicators of Good Evidence Quality for Registries

External validity

- External validity was demonstrated by showing that registry participants were similar to the target population and, to the extent feasible, efforts were devoted to minimizing selection bias (e.g., rules for sequential enrollment were developed and codified in a manner that worked for all sites).
- Completeness of information on eligible patients was evaluated and described.

Internal validity

- For safety studies, a clear and specific approach was used (e.g., solicited vs. unsolicited) to ask about complaints or adverse events.
- Necessary information was collected for relevant key exposures, risk factors, and mitigating or protective factors.
- Exposure data used to support the main research questions were as specific as possible. For example, a specific product, including manufacturer, was identified to the extent feasible.
- Data checks were employed using range and consistency checks.
- For comparative effectiveness and safety,
    - Followup period was reasonably sufficient to capture the main outcomes of interest.
    - Comparators reflect current practice.
    - A sample of data was validated with patient records, (e.g., 10-20% of patients' records were compared with registry data).
    - Followup was reasonably complete for the registry purpose.

Analysis and reporting

- The report describes the methods, including target population and selection of study subjects, compliance with applicable regulatory rules and regulations, data collection methods, any transformation of variables and/or construction of composite endpoints, how missing data were handled, statistical methods for data analysis, and any circumstances that may have affected the quality or integrity of the data. The information was reported with enough detail to allow replication of the methods in another study.
- Results were reported for all the main objectives, including estimates of effect for each.
- Accepted analytic techniques were used; these may have been augmented by new or novel approaches.
- Followup time was described to enable assessment of the impact of the observation period on the conclusions drawn.
- The role and impact of missing data and potential confounding factors were considered.
- The report includes a clear statement of any conclusions drawn from the analysis of the registry's main objectives and any implications of study results. Alternative explanations for the observed results were considered; a variety of factors, including the strength of the association, biases, and temporal relations, were considered before drawing any causal inferences. The practice of making inferences about causation largely on the outcome of tests of statistical significance is discouraged.
- The consistency of results was compared and contrasted with other relevant research.

Table 35. Further Indicators of Registry Evidence Quality (Optional)

External validity

- Eligibility (inclusion and exclusion criteria) was confirmed on enrollment.
- Selection bias was evaluated by describing the representativeness of the actual population in terms of how it was selected, how well the characteristics of the actual population match those of the target population, and to whom the results apply.

Internal validity

- Results that can be confirmed by an unbiased observer—such as death, test results, and scores from validated measures for patient-reported results or clinical rating scales—were used to enhance accuracy and reliability.
- For safety and quality reporting (to third parties),
    - Potential sources of error relating to accuracy and falsification were rigorously evaluated and quantified to the extent feasible (e.g., through database and/or site reviews).
    - Reproducibility of coding was evaluated.

Analysis and reporting

- Validated analytic tools were used for the main analysis. For example, commercially available analytic packages were used. The data elements used in any models were described.
- Effect estimates among meaningful subgroups were described.
- Appropriate statistical techniques were used to address confounding.
- Sensitivity analyses were used to examine and quantify the effect on the association between the ***a priori*** exposure of interest and the outcome(s) by, for example, varying the definitions of exposure, potential confounders, and outcomes.
- For safety studies, the risks and/or benefits of products, devices, or processes under study were quantitatively evaluated beyond simply evaluating statistical significance (e.g., rates, proportions, and/or relative risks, as well as confidence intervals, were reported).
- For studies of comparative effectiveness and safety, contemporaneous data were collected for one or more comparison groups that reflect current clinical practice, when other reasonably accurate and relevant comparative data were not available.

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Contributors

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Appendices

Appendix A. An Illustration of Sample Size Calculations

As a general principle, sample size calculations depend on the study design, the study question, and the scale of measurement of the variables being measured. Indeed, one of the benefits of performing a sample size calculation is the requirement that each of these be specified, thus increasing the likelihood that the proper variables will be measured on the proper patients in the proper manner.

For concreteness, assume that the outcome of interest is a dichotomous variable measured for each patient, such as the presence/absence of a complication associated with carotid endarterectomy (CE). Typically, this literature considers complications within 30 days of the procedure. Nothing essential changes for outcome variables measured on other scales, such as continuous or survival data. The dichotomous outcome (i.e., presence or absence of a complication) is then aggregated across patients into a complication rate (e.g., 9 complications for 300 patients equals a 3-percent complication rate).

For CE, some registry-based designs and study questions that might be of interest include the following. For the purpose of this discussion, *case-mix adjustment* is the incorporation of various patient characteristics believed to influence complications of CE into a mathematical model used to predict the likelihood of these complications. The most natural such model is a logistic regression.

Design 1: For patients at high risk of stroke, perhaps using an operational definition of "symptomatic with 70–99 percent stenosis of the carotid artery," the study question is whether the surgeons within a larger entity (e.g., a national chain of hospitals) are, in aggregate, experiencing complication rates similar to those who participated in the randomized trials demonstrating the efficacy of CE. The reason that this is an open question is that the surgeons and institutions in these randomized trials underwent a high degree of selection, thus raising the concern that surgical outcomes were better than could be expected in usual practice.

The patient inclusion criteria for the registry are selected to be as close as possible to those of the randomized trials; thus, while various characteristics might be collected on each patient, no formal case-mix adjustment is required.

Further, suppose that the 30-day complication rate of CE in the randomized trials was 3 percent. The study question can then be translated into a statistical hypothesis of a one-sample comparison of an observed complication rate vs. a prespecified value. In other words, the null hypothesis is that surgeons within the larger entity are, in aggregate, experiencing complication rates that are the same (3 percent) as those of surgeons who participated in the randomized trials. The final input required to perform the sample size calculation is the complication rate under the alternative hypothesis. For example, if it is determined that the goal of the registry is to have high power to flag results as statistically significant if the true complication rate is 6 percent or higher, then the complication rate under the alternative hypothesis is 6 percent.

In general, the value of the complication rate under the alternative hypothesis is derived using a combination of quantitative and qualitative reasoning. The precise methods used are context dependent and thus not discussed in detail here. In the present example, a cost-effectiveness analysis might suggest that complication rates of 6 percent and above would call into question the efficacy of CE. Given these inputs, it can be shown that the effect size is 0.21, and the sample size required for 80-percent power is approximately 370.

Design 2: Continuing to follow patients at high risk of stroke, now suppose that the goal of the registry is to compare complication rates across hospitals. For simplicity, we continue to assume that patients are sufficiently similar to the comparator patients that no explicit adjustment for case mix is required.

Design 2 is a simple form of benchmarking application. For example, the CE complication rates for each hospital might be reported to a regulatory agency and/or the general public, on the presumption that statistically significant differences between complication rates can be used to identify hospitals with differences in quality of care. The particular danger in this design is that the complication rate for any particular hospital might be estimated with relatively little precision, thus generating results that have more noise than signal. Another danger, discussed later, is that case-mix adjustment is required and not performed, or performed, but not adequately.

We assume that the benchmarking will focus on comparing specific hospitals—i.e., in the underlying statistical model, hospital will represent a *fixed* rather than *random* effect. The null hypothesis is that the complication rates for all the hospitals are identical, and the alternative hypothesis is that the complication rates follow some pattern other than being identical. In this design, specifying the alternative hypothesis of interest is a potentially formidable task. One way to formulate this hypothesis is to focus on outlier hospitals. For example, suppose that there are 10 hospitals in the registry, the overall complication rate among 9 of these is expected to be 3 percent, and the complication rate at the tenth hospital is 10 percent. This information, along with expected number of cases in each hospital, is sufficient to calculate an effect size and thus perform the sample size calculation.

When comparing complication rates among specific hospitals, some adjustment may be made for multiple comparisons—that is, in any group of hospitals, there will always be a hospital with the highest complication rate, and focusing on differences between the outcomes of this particular hospital vs. outcomes of the others will overstate the level of statistical significance. The initial statistical test used to assess the homogeneity of complication rates across all the hospitals in the registry implicitly takes this multiple-comparison problem into account. Subsequent tests, in particular those tests that compare apparent outlier hospitals with others, should include an explicit adjustment for multiple comparisons, and the sample size calculations should reflect the fact that an adjusted comparison is being made.

In practice, the approach to this design might reasonably depend on whether registry data are being collected electronically or manually. If data are being collected electronically, the most sensible policy is to collect information on all CE procedures performed within each hospital and to use the sample size formula as an assessment of whether the registry as a whole is likely to produce results that are sufficiently accurate to support decisionmaking. This assessment can be framed in terms of statistical power, as discussed above, or in terms of precision.

Considering precision, a 95-percent confidence interval for a nonzero complication rate for any hospital is $p \pm 1.96 \text{ sqrt } (pq/n)$, where p is the observed complication rate, $q = 1- p$, and n is the sample size. Supposing that p = 3 percent and n = 300 per hospital, within any particular hospital, the width of this confidence interval is expected to be approximately ± 1.9 percent. If data are being collected manually, and thus the marginal cost of data collection per patient is high, a reasonable policy would be to collect data on a sufficient number of patients in each hospital so that the precision of the estimates of the complication rate within a given hospital would be considered adequate.

As with hypothesis testing, the analysis to derive the width of the confidence interval usually applies a combination of qualitative and quantitative insights. In particular, the question can be reframed as the following: For what values of the complication rate will my decision (whether taken from the perspective of clinical medicine, public health, etc.) be the same? For example, if the decision is the same regardless of where the complication rate falls within the range of 2 to 4 percent, an interval of this width is sufficiently precise.

Unless sample sizes are large, using registries to compare individual hospitals is potentially quite problematic. Although determining the inputs to the power calculations is not always a straightforward task, performing this analysis is quite useful, even if the result is only to suggest extreme caution in the interpretation of differences between hospitals.

Design 3: Continuing to follow patients undergoing CE, now suppose that the goal of the registry is to compare two different versions of the surgical procedure. For simplicity, continue to assume that patients are sufficiently similar to the comparator patients that no explicit adjustment for case mix is required. The following discussion (after including an adjustment for case mix, if appropriate) also applies to comparisons of two different versions of a medical device and similar applications. The key distinctions between this design and Design 2 are that in Design 3 the primary comparison or comparisons can be stated ahead of time and the number of comparisons is relatively small, so that the issue of multiple comparisons can be ignored.

The analytic approach to this design is a logistic regression, with the input file having one record per patient. The outcome variable is the presence or absence of a complication, the categorically scaled control variable is the hospital, and the primary predictor is the categorically scaled coding of the type of surgical procedure (i.e., CE using version A vs. CE using version B). The null hypothesis is that, after accounting for any differences in hospitals, the two different versions of the procedure have identical complication rates. The alternative hypothesis is that the rates differ by a specified amount, this amount being the *minimum clinically significant difference* interpreted to be of concern. Power calculations proceed in the same fashion as for logistic regression with multiple predictors.

The main pitfall in this design is that patients who receive version A of the surgical procedure might differ from those who receive version B of the procedure along some dimension that has an impact on outcomes. (This pitfall is discussed in more detail under Design 4.)

In this application, the null and alternative hypotheses are sometimes structured the same way as in an equivalence trial—that is, differences in complication rates are not expected, and the goal of the study is to demonstrate that complication rates for the two versions of the surgical procedure are similar within a certain level of precision. The structure of the analysis is not fundamentally different. Indeed, sample size

calculations for equivalence trials are sometimes not performed within a hypothesis-testing framework but instead by identifying a sample size of sufficient magnitude to make the confidence interval for the difference in the complication rates between the two versions of the surgical procedure a certain width. For simplicity of presentation, let us assume from now on that any equivalence-trial-type calculations can be reframed into confidence-interval format, and thus need not be discussed separately.

Design 4: Continuing to follow patients at high risk of stroke, and continuing to assume that the goal of the registry is to compare two different versions of the surgical procedure, now additionally assume that this comparison will include an adjustment for case mix. Within the logistic regression paradigm, variables used to adjust for case mix are accounted for as covariates (i.e., additional predictors). Alternatively, propensity-scoring methods could be used to adjust for those variables that predict the assignment of patients to particular versions of the procedure. For concreteness, let us focus on logistic regression. In order to perform a sample size calculation for a logistic regression, the analyst must specify the predictive ability of the covariates and the odds ratio associated with the predictor of interest. (For example, version B of the procedure might increase the odds of complications by a factor of 1.5.) Once these inputs are specified, the sample size calculation is straightforward.

Both the logistic-regression and propensity-scoring approaches suffer from the fundamental drawback that they can adjust only for covariates that are observed. In particular, if there are variables that predict outcome that are unmeasured (e.g., a physician's assessment of a patient's likelihood to comply with treatment, or stroke in evolution not included in the administrative database used as the source of data for the registry), then the comparison between the two versions of the surgical procedure is potentially biased. Accordingly, before proposing to use a registry to compare complication rates (e.g., across different versions of a procedure or a device) or other outcomes, it is critical to determine that the following three conditions do not all hold: (1) a patient, provider, system, or other characteristic affects the complication rate; (2) this characteristic is unmeasured within the registry; and (3) there is a reasonable likelihood that this characteristic might be differentially distributed across the different versions of the procedure or the device. If all three conditions (in epidemiologic terms, the conditions for *confounding*) hold, use of the registry to compare outcomes is potentially dangerous.

Critical to Designs 1–4 is the assumption that the CE complication rate is stable over time. Thus, for example, it is appropriate to use the registry to estimate a single complication rate associated with version A of the procedure, estimate another single complication rate associated with version B of the procedure, and compare the rates. On the other hand, if the technology of CE (e.g., physical materials, surgical technique) is improving, then the registry should continue to monitor the performance of CE over time. Such an ongoing monitoring function seems particularly relevant for medical devices and similar applications.

Even when the associated technology is assumed stable, some registries are intended to provide ongoing assessments of outcomes. For example, in a quality assurance context, CE complication rates might be assessed at individual hospitals on an annual basis (e.g., in order to check for problems that have recently arisen). On the other hand, a registry whose purpose is to assess whether the complication rates that were observed in randomized trials could be achieved in usual practice could be designed with a sunset provision to cease operation once this question is answered. The latter type of registry might, for example, support a coverage decision by the Centers for Medicare & Medicaid Services.

Having an ongoing monitoring function induces additional analytical complications, among others a multiple-comparisons problem. Traditional statistical power calculations are performed under the assumption that the sample size is fixed and that, unless otherwise noted, multiple comparisons are not a major issue. Sequential testing methods associated with randomized trials (where, for example, the type I error of .05 is apportioned into an early test with alpha = .001 and a subsequent test with alpha = .499) are not appropriate for this particular design, since most of these methods assume that the maximum sample size is fixed. Some methods assume that what is fixed is not the number of patients but the number of events, but these methods are also inappropriate for registry applications.

Design 5: Suppose the goal is to estimate the complication rate associated with CE at multiple time points for the foreseeable future. Control chart methodology might reasonably be applied to this class of problems. This methodology, often used in the quality assurance and quality improvement context, was originally developed for industrial applications. In this example, the null hypothesis, under which the system in question is "in control," is that the CE complication rate remains at the desired value of 3 percent throughout the entire followup period. Samples are taken at given points in time (e.g., monthly). As an example, if these monthly samples are of size 100, then the standard error is approximately 1.7 percent. The analyst then creates a *control chart* by plotting these monthly complication rates over time and forming *channels* based on the standard error. In this example, the channel extending from the point estimate to 1 standard error above the point estimate is 3 percent to 4.7 percent.

Once the basic control chart— which goes by different names depending on the scale of measurement of the outcome variable—is formed, the plot is checked for various violations of the null hypothesis of constant complication rates. The set of possible violations to be flagged as statistically significant might include (1) any observation more than 3 standard errors from the mean; (2) two of three consecutive observations more than 2 standard errors from the mean; (3) eight observations in a row that increase or decrease; and (4) eight observations in a row on one side of the mean. These rules of thumb implicitly take into account the multiple-comparisons problem by requiring noteworthy departures from the null hypothesis in order to be flagged; they are also based on the observed properties of physical machines as they fall out of adjustment: suddenly breaking down and producing an extreme outlier, or gradually heating and thus producing sequentially higher readings. Complication rates of CE might or might not follow the properties of physical machines, but the decision rules from control chart methodology are at least a good place to start.

Appendix B. Copyright Law

Copyright law confers exclusive legal rights to the owner of the copyright.[1] The exclusive rights of copyright may be sold, assigned (transferred), or licensed (limited transfer of rights for use on specific terms or conditions) to others; these rights may also be waived (quit claim). Licensing ordinarily consists of a private agreement governed by contract rather than copyright law.[2]

However, the exclusive rights conferred by copyright to prepare derivative works and distribute copies of a health information registry may be limited by regulatory requirements. Privacy Rule restrictions may limit data use, reuse, and disclosures or may require additional patient authorizations for subsequent research use. The conditions of institutional review board (IRB) approval under the Common Rule may also limit reuse and further disclosure of registry data. The terms of patient authorization and consent, a data use agreement, or a business associate agreement may modify the scope and nature of rights protected by copyright law. These limitations can be avoided by the use of de-identified health information, as defined by the Privacy Rule, plus information that is not subject to the Common Rule, if they suffice for the scientific or other purposes of the registry. Without resort to copyright protections, State laws may directly restrict access to registry data, as well as the use and disclosure of data from registries developed by public health agencies.

Formal copyright registration[3] with the U.S. Copyright Office is not necessary but may be desirable for registries anticipated to have commercial value. The owner of a copyright is generally the author[4] or author's employer; ownership of the copyright for a compilation is not ownership of the underlying facts or data.[5] Copyright law presumes that an employer owns the copyright in materials created by an employee within the scope of his or her employment as a "work made for hire."[6] Institutional policies and procedures frequently prescribe whether the registry developer, his or her employer, or a funding agency owns the copyright. Employee manuals often contain an employer's position on the intellectual property created by employees. Research institutions frequently reserve the right to the intellectual property produced by their employees. Intellectual property issues are explicitly negotiated in most sponsored research contracts. Authors of a joint work are co-owners of copyright in the work.[7]

Several factors determine whether the use of a registry protected by copyright for scholarship, research, or certain other purposes is within the statutory fair use limitation on copyright.[8] In general, these factors will support subsequent uses of registry data for research, even though it may be protected by copyright. In any given set of circumstances, a specific analysis of the statutory factors is necessary to determine whether use is likely to be viewed within the fair use limitation on copyright.[9]

Copyright law may provide some legal protections for compilations such as health information registries. The extent of this protection depends on the specific characteristics of the registry. In general, the concept of ownership does not comfortably apply to health information, even when limited to copyright. Nevertheless, some registry developers may want to consider adding the legal protections of copyright to reinforce controls on access to and use of registry data. Registry developers may also encounter copyright protections on health information held by health care providers. Use of health information protected by copyright for research purposes may constitute fair use under copyright law.

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Appendix C. Relevant Entities in Health Information Technology Standards

The Clinical Data Interchange Standards Consortium, or CDISC, is a multidisciplinary nonprofit organization that is focused specifically on medical research and that works toward developing and supporting global, platform-independent data standards that enable information system interoperability. It is a membership organization made up of more than 170 academic research centers, global biopharmaceutical companies, technology and service providers, and institutional review boards (IRBs).[1] CDISC has established standards to support the acquisition, exchange, submission, and archiving of clinical research data and metadata, such as case report tabulation data definitions, submission data, and operational data modeling; these standards are intentionally vendor neutral, platform independent, and freely available. CDISC has formed key partnerships with other standards bodies, vendors, and research groups to further the creation and use of these and other industry standards. CDISC's Healthcare Link project is an initiative that specifically focuses on the mission of interoperability between health care and clinical research.

Health Level Seven, or HL7, is an American National Standards Institute (ANSI)–accredited non-profit organization that produces specifications and protocols for clinical and administrative health care data.[2] HL7 is a global organization with corporate and individual membership consisting of providers, vendors, payers, consultants, and government groups. Like CDISC, HL7 does not develop software, but instead creates specifications. HL7's original specification was a messaging standard that enables disparate health care applications to exchange key sets of clinical and administrative data.[3] This standard defines the structure and content of the messages that are exchanged between systems in either batch mode, which facilitates transfer of a collection of individual messages labeled by a single header, or interactive mode, which transmits a single message. HL7 then extended this idea to a Clinical Document Architecture (CDA), which is designed to support standards for storing and retrieving file-level information such as electronic health records (EHRs).[3] The Reference Information Model (RIM) then specifies the details, results, and contexts of clinical informatics by defining subject areas, classes, attributes, use cases, and trigger events (such as a followup clinical visit).[4] HL7 also houses important specifications and tools relating to electronic documentation of standards, for example, the Continuity of Care Document (CCD).

The Healthcare Information and Management Systems Society, or HIMSS, is an industry membership organization that focuses on knowledge sharing, advocacy, and collaboration among its members. HIMSS is a longstanding advocate of using information management systems to improve health care, and represents a large portion of the industry (more than 20,000 individuals and 350 corporations).[5] HIMSS plays a critical role in this discussion through the HIMSS Electronic Health Record Association, and also through its role in partnering with two other key standards groups: the Health Information Technology Standards Panel (HITSP) and Integrating the Healthcare Enterprise (IHE).

The HIMSS Electronic Health Record Association (EHRA) is a trade association specifically made up of EHR companies. This association is a key player in the interoperability discussion. EHRA focuses on creating interoperable EHRs in hospital and ambulatory care settings by providing a forum and structure for EHR leaders to work toward standards development, interoperability, the EHR certification process, performance and quality measures, health information technology legislation, and other EHR issues.[6]

Integrating the Healthcare Enterprise (IHE) is an initiative sponsored by HIMSS, the Radiological Society of North America (RSNA), and the American College of Cardiology (ACC).[7] It is designed specifically to bridge the gap between existing standards and the implementation of integrated systems. IHE does this by creating *Profiles*, which specify precisely how standards are to be used in integration implementations. It is important to note that IHE does not develop standards; instead, it provides a link between the standards that exist and the problems among the industry that need to be solved. The initiative is focused on eliminating ambiguities, reducing configuration and interfacing costs, and ensuring a higher level of practical interoperability for users and developers of health care information technology as they implement standards-based communication between systems and then perform tests to determine that the implementation conforms to the specifications.[8] In recent years, IHE has developed the Patient Identifier Cross Referencing (PIX) Integration Profile, which supports the cross-referencing of patient identifiers from multiple domains,[9] and the Patient Demographics Query (PDQ) Integration Profile, which facilitates the querying of a patient database to retrieve demographics data.[10] Standards from different organizations that achieve the same goal can be inserted into an IHE Profile, and IHE will then produce technical specifications that can be used by developers and vendors to build products compliant with those standards. Because of IHE's practical approach, its value has been recognized by other standards organizations, particularly CDISC. For example, IHE has defined a simple four-step process that carries a specific problem from problem definition, through implementation and testing, to the real world:

1. Identify interoperability problem.
2. Specify Integration Profiles.
3. Test systems at Connectathon (an annual weeklong interoperability-testing event); demo at HIMSS Interoperability Showcase.
4. Implement in real world.

The Healthcare Information Technology Standards Panel serves as a partnership between the public and private sectors with the purpose of identifying a widely accepted set of standards for interoperability of health care applications. HITSP is funded by the U.S. Department of Health and Human Services (HHS), administered by ANSI, and tightly partnered with HIMSS; Federal agencies are mandated to use interoperability standards that have been harmonized by HITSP.[11]

The Certification Commission for Health Information Technology (CCHIT) is a private nonprofit organization with the "sole public mission of accelerating the adoption of robust, interoperable health information technology by creating a credible, efficient certification process."[12] It is divided into workgroups that address the standards for specific functional areas such as ambulatory care, behavioral health, personal health records, and cardiovascular care. Since being recognized as a certifying body by HHS in 2006, it remains the only federally approved organization to certify health information technology products and systems.

The Regenstrief Institute, Inc. is an informatics and healthcare research organization and a joint enterprise of the Regenstrief Foundation, Inc., the Indiana University School of Medicine, and the Health and Hospital Corporation of Marion County. Regenstrief is active in developing healthcare informatics standards, including the widely-used Logical Observation Identifiers Names and Codes (LOINC®) terminology. It is currently conducting research for the Agency for Healthcare Research and Quality (AHRQ) entitled "Advancing Patient Identity Management in the Context of Real-World Health

Information" which focuses on "creat[ing] a more robust and efficient global patient matching algorithm."[13]

Table C-1. Relevant Entities in Health Information Technology Standards

Group	Year established	Number of members	Mission	Relevant standards/specifications
CDISC	2000	>290 (corporate)	Developing and supporting data standards.	CDASH
HL7	1987	>4,000	Producing specifications and protocols for clinical and administrative health care data.	CDA, RIM, CCD
HIMSS	1961	>570 (corporate) >44,000 (individuals)	Knowledge sharing, advocacy, and collaboration.	
EHRA	2004	~40 (corporate)	Creating interoperability between existing EHRs.	EHRA Interoperability Roadmap
IHE	1997	>540 (organizations)	Providing a link point between the standards that exist and the problems among the industry that need to be solved.	RFD, CRD
HITSP	2005	>550 (corporate and organizations)	Partnering with public and private sectors to achieve standards to support interoperability among health care software applications.	TP50, C76
CCHIT	2004	94 products certified under 2011/2012 CCHIT criteria	Defines the requirements for an EHR to be certified in the United States.	CCHIT certification criteria (available at ww.cchit.org/certify)
Regenstrief Institute	1969	>50 (investigators)	Improvement of health through research that enhances the quality and cost-effectiveness of health care.	LOINC®

***Note**: C76 = HITSP Case Report Pre-Populate Component. CCD = HL7 Continuity of Care Document. CCHIT = Certification Commission for Health Information Technology. CDA = HL7 Clinical Document Architecture. CDASH = Clinical Data Acquisitions Standards Harmonization. CDISC = Clinical Data Interchange Standards Consortium. CRD = IHE Clinical Research Data Capture. EHR = electronic health record. EHRA = Electronic Health Record Association. HIMSS = Healthcare Information and Management Systems Society. HITSP = Healthcare Information Technology Standards Panel. HL7 = Health Level Seven. IHE = Integrating the Healthcare Enterprise. LOINC = Logical Observation Identifiers Names and Codes. RFD = IHE Retrieve Form for Data Capture. RIM = HL7 Reference Information Model. TP50 = HITSP Retrieve Form for Data Capture Transaction Package.*

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Appendix D. Linking Clinical Registry Data With Insurance Claims Files

A research project is being designed to compare the effectiveness for treating diabetes of one class of medication, or one specific generic medication within the class, to another. The results should provide scientific evidence for patients, physicians, and policymakers to use to make decisions about the use of these drugs.

Registry developer A will collect limited datasets of information on patients discharged with a diagnosis of diabetes from hospitals in three States. These limited datasets do not include patient names or direct identifiers, and so are not considered individually identifiable health information under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The registry developer has institutional review board (IRB) approval to use the data for research purposes. The hospitals will provide the datasets to group B under a data use agreement that complies with the HIPAA Privacy Rule.

Group B intends to perform probabilistic matching of the registry data to a health insurance claims database to determine diabetes treatment outcomes. Registry developer A and research group B have entered into a formal collaboration for this research project.

The health insurance database will be derived from the claims data of multiple health plans operating in the same three States. The insurers' original datasets include direct beneficiary identifiers and constitute protected health information under the HIPAA Privacy Rule. Because the registry contains only limited datasets, the claims data collected in the insurance database will have to be linked to the registry data using probabilistic matching techniques.

Consequently, the research project will use only a limited dataset of health insurance claims data to create the link with the registry data. The health insurance companies will provide the limited datasets of claims information to group B under data use agreements that comply with the HIPAA Privacy Rule.

The common data elements for the insurance database and the registry that will be used for linkage are date of birth, gender, race, hospital ID, State of hospital, date of admission, date of discharge, date of death (if the patient died), ICD-9 (International Classification of Diseases, 9th Revision) code for primary diagnosis for the index hospitalization, primary procedure code for the index hospitalization, and ZIP Code for the patient's address.

In order to protect the identity of the hospitals, the researchers were asked to sign a confidentiality agreement that specifically defined the registry operator's proprietary information. Such proprietary information included the names or other identifiers of hospitals or other health care facilities participating in the registry. The researchers were precluded from using the names or other distinguishing characteristics of the hospitals in any public document, including publications or marketing materials. The confidentiality agreement did allow the researchers to retain an identifier number for each hospital, as long as that number identified only generic characteristics and excluded any information about the hospital that would enable anyone to identify the specific hospital. For example, the researchers could not retain information that classified a particular hospital with a number that identified it as an academic

teaching hospital based in a particular State with a certain number of beds, since in many instances the identity of the hospital could be derived from such information. Due to the potential contractual liability that may arise, the possibility of identifying participating hospitals is a critical issue.